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United States Patent [19]
Chouinard

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[45] **Date of Patent:** **Dec. 5, 2000**

[54] **STENT-GRAFT-MEMBRANE AND METHOD OF MAKING THE SAME**

[75] Inventor: **Paul F. Chouinard**, Roseville, Minn.

[73] Assignee: **Schneider (USA) Inc**, Plymouth, Minn.

[21] Appl. No.: **09/134,859**

[22] Filed: **Aug. 14, 1998**

[51] Int. Cl.⁷ **A61F 2/06**

[52] U.S. Cl. **623/1.44; 623/1.46**

[58] Field of Search **623/1, 1.18, 1.39,
623/1.44, 12; 606/198, 195; 87/33; 428/36.92**

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Primary Examiner—Michael J. Milano

Assistant Examiner—Hieu Phan

*Attorney, Agent, or Firm—Frederick W. Niebuhr, Esq.;
Larkin, Hoffman, Daly & Lindgren, Ltd.*

[57] **ABSTRACT**

A braided self-expandable stent-graft-membrane made of elongated members forming a generally tubular body. A membrane layer and graft layer are disposed on an endoprosthesis such as a stent. The membrane layer is substantially impermeable to fluids. The outermost layer is biocompatible with the body tissue. The innermost layer is biocompatible with the fluid in the passage. An embodiment includes a graft layer disposed on the inside of a stent and a membrane layer disposed on the outside of the stent. The innermost layer is biocompatible with the fluid in the passage. The stent-graft-membrane is used at a treatment site in a body vessel or organ where it is desirous to exclude a first fluid located outside the endoprosthesis from reaching a second fluid located in the lumen. The membrane may be made of silicone or polycarbonate urethane. The graft may be braided, woven, spun or spray-cast PET, PCU, or PU fibers. The layers may include ePTFE or PTFE.

44 Claims, 11 Drawing Sheets

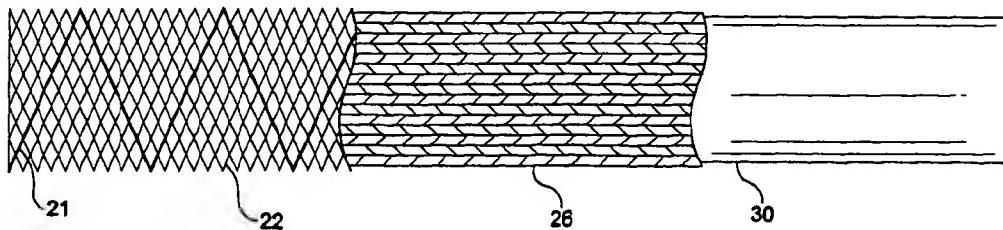


FIG-1

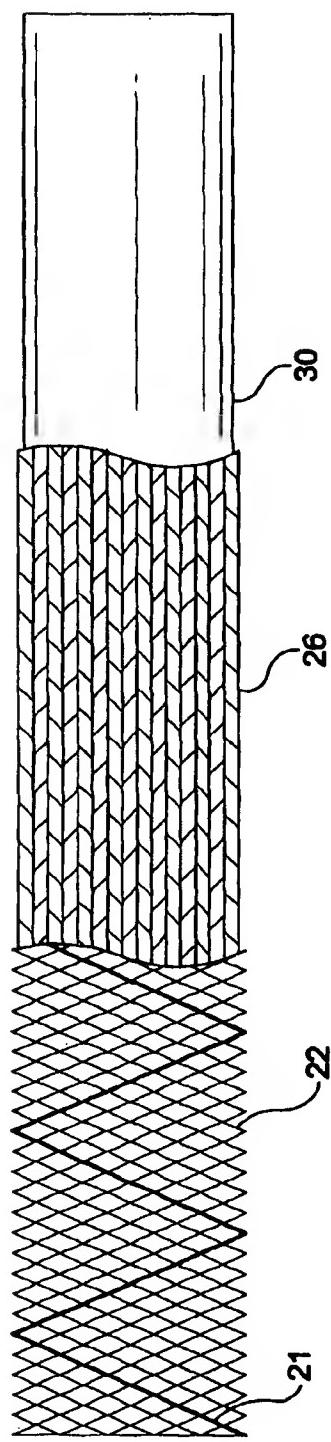


FIG-1A

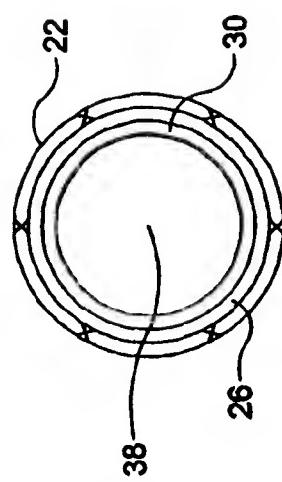


FIG-2

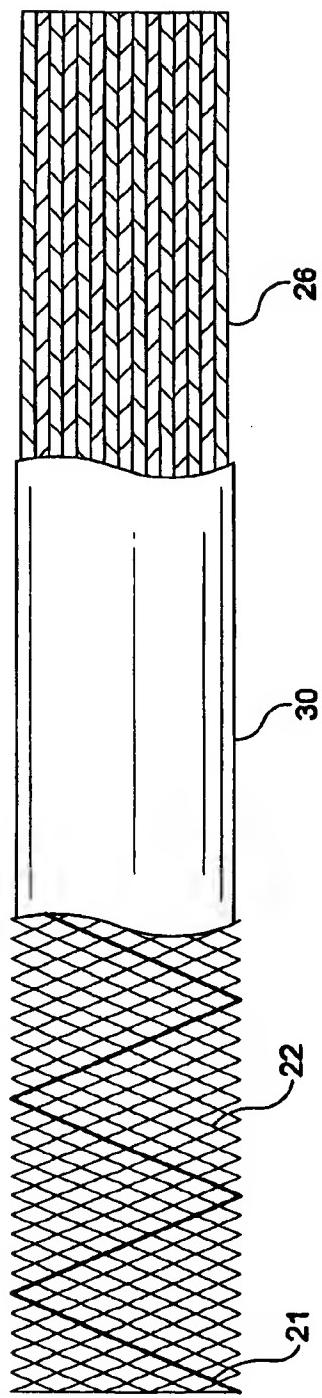


FIG-2A

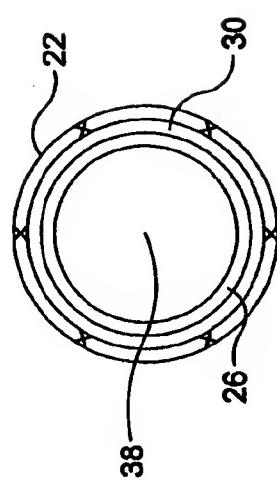


FIG-3

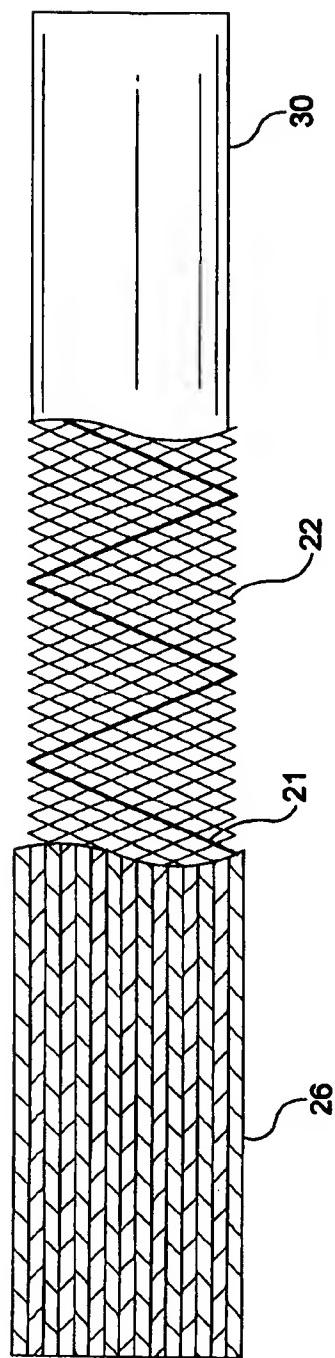


FIG-3A

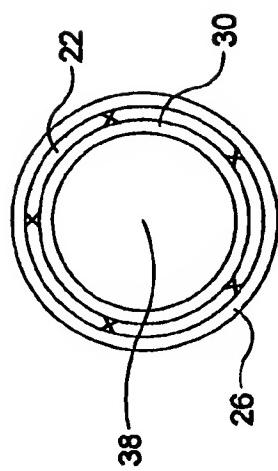


FIG-4

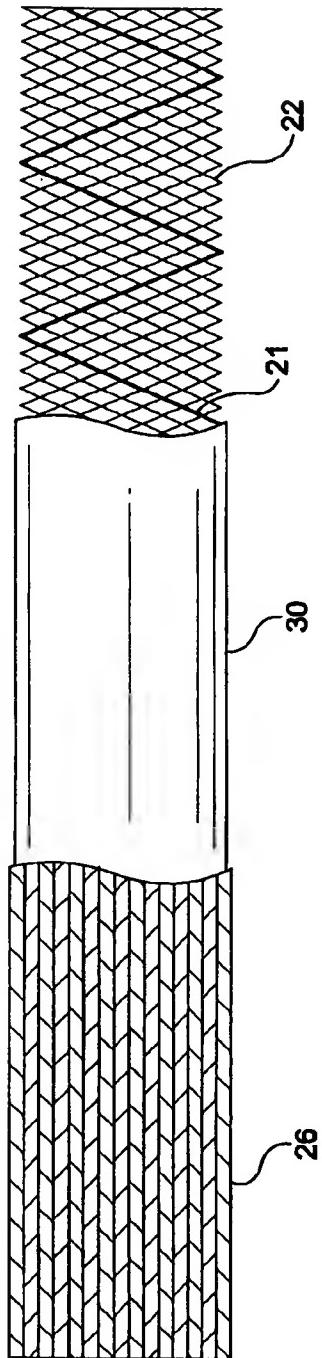


FIG-4A

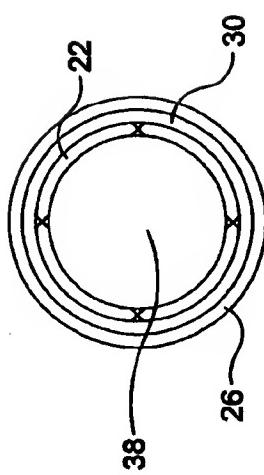


FIG-5

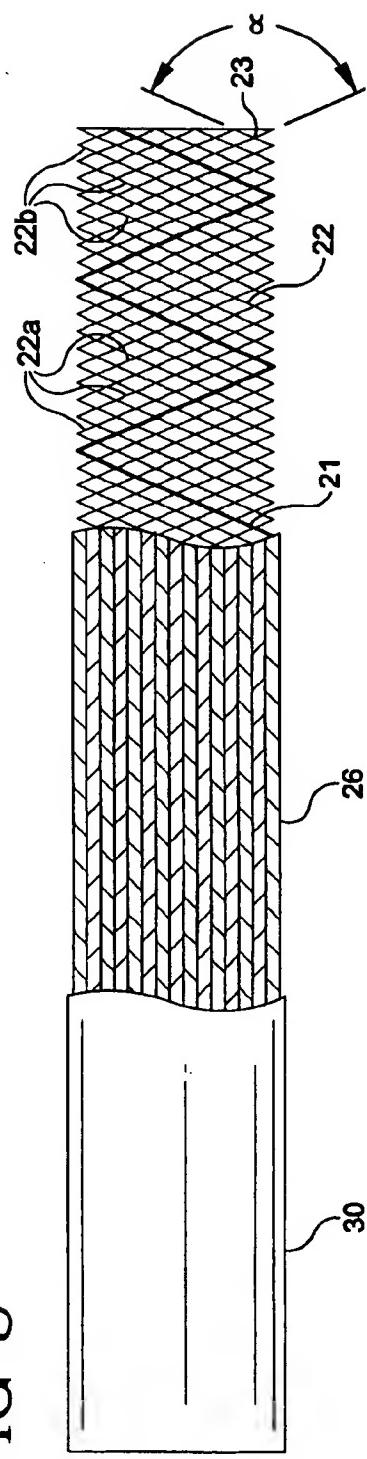


FIG-5A

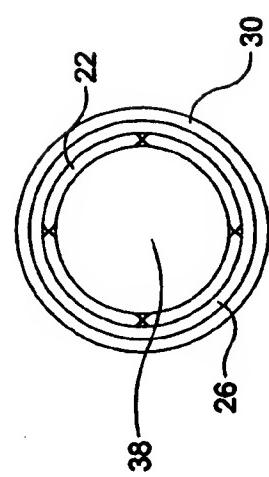


FIG-6

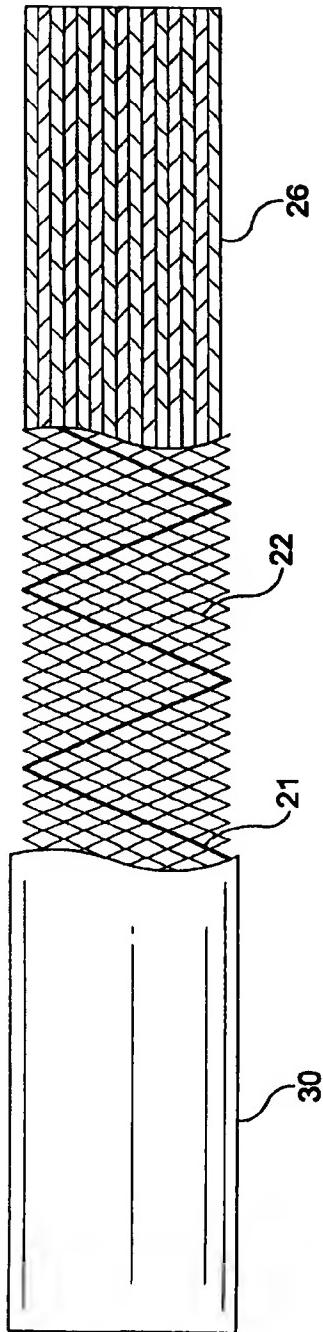


FIG-6A

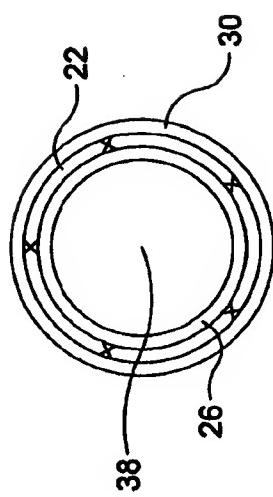


FIG-7

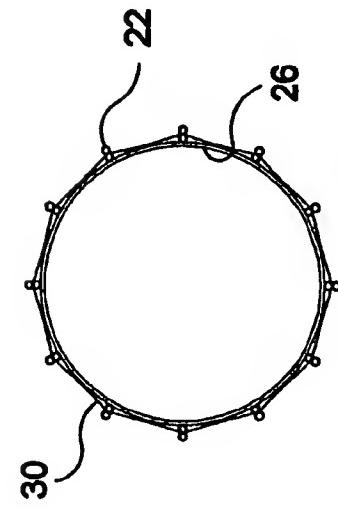


FIG-8

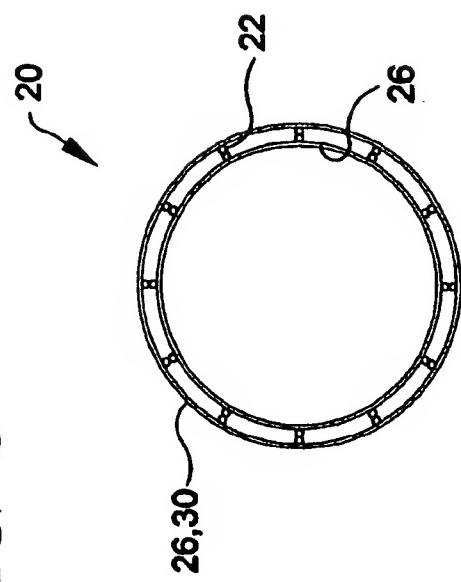


FIG-9



FIG-10

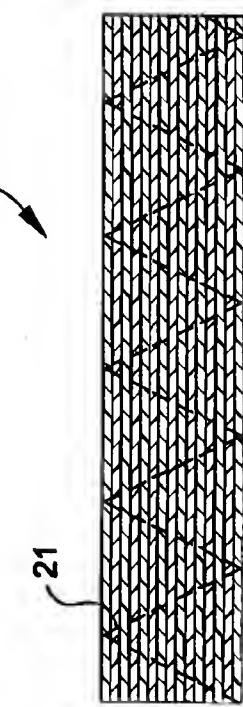


FIG-11

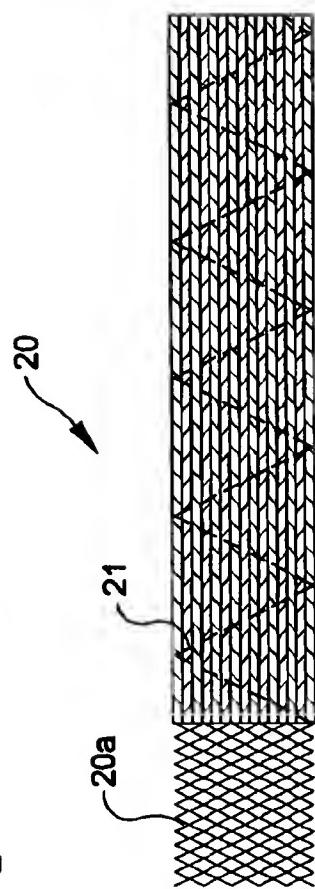
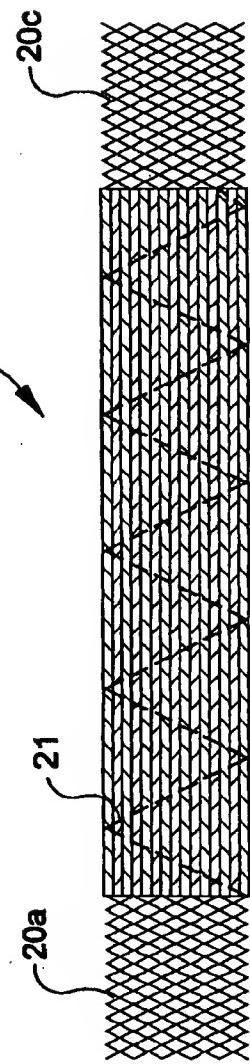


FIG-12



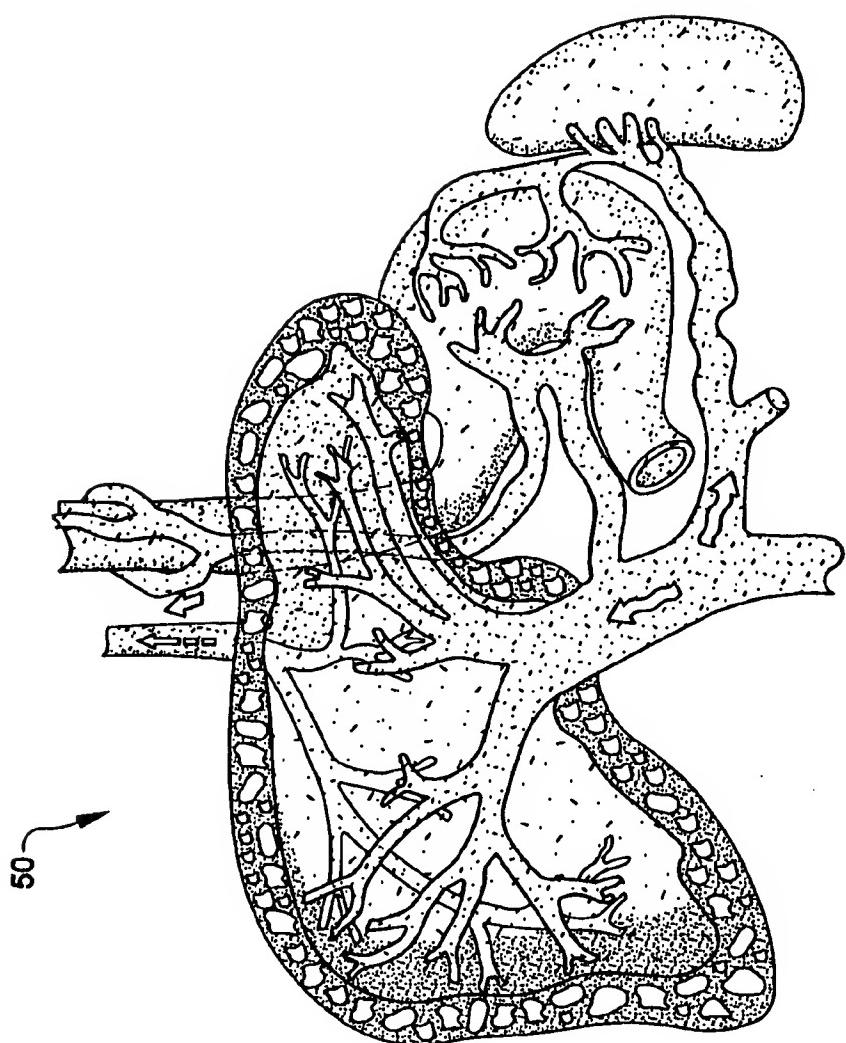


FIG-13

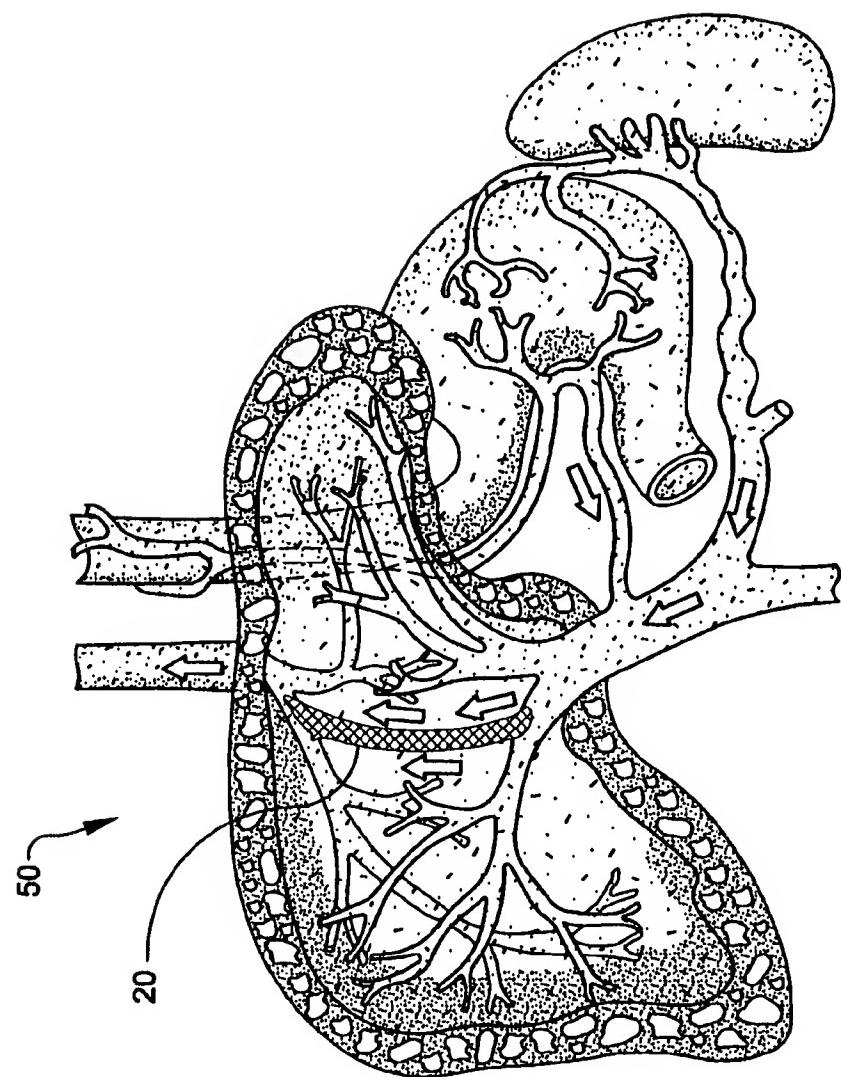


FIG-14

**STENT-GRAFT-MEMBRANE AND METHOD
OF MAKING THE SAME**

FIELD OF THE INVENTION

The present invention relates to a stent-graft-membrane for placement at a treatment site within a body vessel or organ to enhance and direct fluid flow therethrough and a method of making the same. More particularly, the invention relates to an implantable endoprosthesis such as a stent combined with a generally impermeable membrane layer and a permeable graft layer. The graft and the membrane provide biocompatibility with tissue at the treatment site and provide biocompatibility with fluid in the lumen.

BACKGROUND OF THE DISCLOSURE

Intraluminal implantable endoprostheses such as self expanding stents, grafts and stent-grafts are known and are, for example, shown in U.S. Pat. Nos. B1 4,954,126; 5,116,360; 5,133,742; 5,591,226; 5,653,747; and 5,679,470. A covered stent is described in International Publication Number WO 94/24961. A polyurethane is described in U.S. Pat. No. 4,810,749. A porous implantable material is described in U.S. Pat. No. 4,475,972. A method of forming an implantable graft is described in U.S. Pat. No. 4,738,740.

U.S. Pat. No. B1 4,655,771, entitled, *Prosthesis Comprising Expandible or Contractile Tubular Body*, discloses a prosthesis comprising a flexible tubular body for transluminal implantation.

U.S. Pat. No. 5,061,275, entitled, *Self-Expanding Prosthesis*, discloses a resilient, elastic self-expanding prosthesis comprising a flexible tubular body.

U.S. Pat. No. 5,645,559, entitled, *Multiple Layer Stent*, discloses a radially self-expanding stent having multiple layers that includes a medial region and proximal and distal cuffs having diameters greater than the medial region diameter when the stent is in the relaxed state. A silicone coating circumscribes at least the medial region of the stent.

U.S. Pat. No. 5,718,159, entitled, *Process for Manufacturing Three-Dimensional Braided Covered Stent*, discloses a prosthesis having a flexible tubular three-dimensionally braided structure of metal or polymeric monofilaments, and polymeric multifilament yarns.

U.S. Pat. No. 5,741,333, entitled, *Self-Expanding Stent For A Medical-Device To Be Introduced Into A Cavity Of A Body*, discloses a self-expanding stent.

U.S. Pat. No. 5,755,774, entitled, *Bistable Luminal Graft Endoprosthesis*, discloses a luminal graft endoprosthesis or endovascular graft which is capable of dilation and support functions and suitable for the endoluminal repair of vascular lesions and the like. An expandable support or stent is combined with a tubular graft made of a material having two unstressed conditions to provide a combined stent-graft wherein the graft material is secured to either or both of the internal or external surfaces of the stent.

U.S. Pat. No. 5,534,287, entitled, *Methods for Applying an Elastic Coating Layer on Stents*, discloses a coated stent comprising a cylindrical wall formed by meshed wires and a covering layer of elastic material extending on a portion of its length, with an outer surface, and totally embracing the wire mesh.

U.S. Pat. No. 4,850,999, entitled, *Flexible Hollow Organ*, discloses a flexible hollow organ, especially a vascular prosthesis intended for implantation in the human or animal body parts. The hollow organ includes a flexible prosthetic tube serving for a throughflow of a medium or which

consists of such a prosthetic tube. A wall of the prosthetic tube exhibits at least one braided hose of flexible, elastic threads produced as a hollow meshwork.

A stent-graft is described in U.S. patent application Ser. No. 08/640,253, entitled "Cobalt-Chromium-Molybdenum Alloy Stent and Stent Graft", filed Apr. 30, 1996.

A stent-graft is described in U.S. patent application Ser. No. 08/993,985, entitled, *Stent-Graft with Bioabsorbable Structural Support*, filed Dec. 18, 1997.

A stent-graft is described in U.S. patent application Ser. No. 08/946,906 entitled, *Stent-Graft with Braided Polymeric Sleeve*, filed Oct. 8, 1997.

All references cited herein are incorporated herein by reference in their entireties for all purposes.

SUMMARY OF THE INVENTION

The stent-graft-membrane of the present invention has at least three layers and is intended for treatment of vascular lumens, non-vascular lumens or organs in the body. The three layers include a structural stent layer, a graft layer and a membrane layer. The three layers may be formed in different combinations of layers. A need exists for a stent-graft-membrane of the present invention having layers with surfaces that are selected to be biocompatible with the tissue or fluid for which they are associated with while treating vessels or organs. Biocompatibility means that the implant is accepted by the host tissue and does not create an adverse biological response.

The stent-graft-membrane may advantageously be used in a variety of medical applications including intravascular treatment of stenoses, aneurysms or fistulas; maintaining opening in the urinary, biliary, tracheobronchial, esophageal, renal tracts, vena cava filters; repairing abdominal aortic aneurysms; or repairing or shunting damaged or diseased organs.

In sum, the invention relates to an implantable endoprosthesis including a first number of elongated members wound helically in a first common direction and crossing a second number of elongated members wound helically in a second common direction. The crossings of the first and second elongated members define an angle and form a generally tubular body having an inside surface, outside surface, ends and a middle portion. The first and second elongated members are braided in a braid pattern and are configured to be constrainable to a reduced diameter and self-expandable to an increased diameter. The tubular body is disposed at a treatment site in a body vessel or organ having body tissue. A passage extends in a longitudinal direction at least partially through the generally tubular body. The passage at least partially contains a fluid in the lumen and directs flow. One or more outside layers are disposed over or on at least a portion of the outside surface of the tubular body. An outermost layer of the one or more outside layers is biocompatible with the body tissue. One or more inside layers are disposed over or on at least a portion of the inside surface of the tubular body. An innermost layer of the one or more inside layers is biocompatible with the fluid in the passage. At least one of the one or more outside layers or the one or more inside layers are substantially impermeable to fluids. The inside layer or the outside layer may each include one or more layers. The one or more inside and outside layers may include one or more membrane layers having an average permeability ranging from about 0 cc/cm²/min. to about 100 cc/cm²/min. and/or one or more graft layers having an average permeability ranging from about 50 cc/cm²/min. to about 5000 cc/cm²/min. The outside layer

may be a film or membrane made of silicone or polycarbonate urethane and the inside layer may be a graft made of braided PET. The inside layer may be ePTFE or PTFE. The implantable endoprosthesis may be designed to provide structural support to a body vessel for a period of time and substantially separate a first body fluid located outside the endoprosthesis from a second body fluid located in the passage. The implantable endoprosthesis may be disposed at a Transjugular Intrahepatic Portosystemic Shunt (TIPS) treatment site. At a TIPS treatment site, the first fluid may include bile and the second fluid may include blood. The braided implantable endoprosthesis may include an opening defined by each end of the generally tubular body. The tubular body may be made of metal, plastic, bioabsorbable or other synthetic or natural materials. The tubular body may have a braid angle or filament crossing angle of between about 65 degrees and 155 degrees.

The invention also relates to an implantable endoprosthesis including a first set of filaments each of which extends in a configuration along a center line and having a first common direction of winding. A second set of filaments each extends in a configuration along a center line and having a second common direction of winding. The first and second filaments form a stent. One or more membrane layers having a first average permeability are disposed over or on at least one of an inside, interstices, or outside surface of the stent or a graft. One or more graft layers having a second average permeability are disposed over or on at least an inside, interstices, or outside surface of the stent. The first and second set of filaments, and the one or more membrane layers and graft layers form a self expanding structure having one or more layers including an inside layer, middle layer, outside layer, embedded layers or combinations thereof, inside surface, outside surface, proximal end, distal end, and a lumen. The inside surface is selected or configured to be substantially biocompatible with a fluid flow through the body lumen and the outside surface is selected or configured to be substantially biocompatible with a body tissue. The first average permeability may be less than the second average permeability. The one or more membrane layers may have an average permeability ranging from about 0 cc/cm²/min. to about 100 cc/cm²/min., and the one or more graft layers may have an average permeability ranging from about 50 cc/cm²/min. to about 3000 cc/cm²/min. The one or more graft layers may include polyethylene terephthalate (PET), expanded polytetrafluoroethylene (ePTFE), polycarbonate urethane (PCU), polyurethane (PU), or combinations thereof. The one or more membrane layers may include siloxane polymers, polyurethane polymers, polycarbonate urethanes, PTFE, ePTFE, or combinations thereof. The one or more membrane layers may be disposed between the graft and the stent. The one or more graft layers may be disposed between the membrane and the stent. The stent may be disposed between the one or more membrane layers and the one or more graft layers. The layers may be bonded with an adhesive. The stent may be made of poly (alpha-hydroxy acid), PGA, PLA, PLLA, PDLA, polycaprolactone, polydioxanone, polyglucanone, polylactic acid-polyethylene oxide copolymers, modified cellulose, collagen, poly (hydroxybutyrate), polyanhydride, polyphosphoester, poly (amino acids), or combinations thereof. The filaments may include Elgiloy®, stainless steel, nitinol, drawn filled tube (DFT), platinum, tungsten, tantalum, or combinations thereof. The graft layers may include a plurality of interwoven fibers, mono-filaments, multi-filaments, or yarns. The membrane layers may include a film, sheet, or tube. The implantable endoprosthesis may substantially exclude a first

fluid located outside the surface of the implantable endoprosthesis from reaching a second fluid located in the lumen. The inside layer may be made of a PET polymer. The outside layer may be made of a silicone elastomer. The silicone elastomer may be a coating. The outside layer may be made of a polymer that is resistant to fluid permeability or resistant to tissue ingrowth.

The invention also relates to a method of making a stent-graft-membrane including: forming a first number of elongated members wound helically in a first common direction and crossing a second number of elongated members wound helically in a second common direction. The crossing of the first and second elongated members define an angle and form a generally tubular body having an inside surface, outside surface, ends and a middle portion. The first and second elongated members are braided in a braid pattern and are designed to be constrainable to a reduced diameter and self-expandable to an increased diameter. The tubular body is adapted to be disposed at a treatment site in at least one of a body vessel or organ having body tissue; forming a passage extending in a longitudinal direction at least partially through the generally tubular body. The passage is adapted to at least partially contain a fluid; forming one or more outside layers on at least a portion of the outside surface of the tubular body. An outermost layer of the outside layers is biocompatible with the body tissue; forming one or more inside layers on at least a portion of the inside surface of the tubular body. An innermost layer of the inside layers is biocompatible with the fluid in the passage. At least one of the outside layers or the inside layers is substantially impermeable to a fluid.

The invention also relates to a method of making a stent-graft-membrane including: braiding bioabsorbable filaments to form a tubular braid. The braid having a braid angle; disposing the braid on a mandrel; annealing the braid for a predetermined time to form an annealed stent; removing the stent from the mandrel, the stent having a filament crossing angle; forming a graft having an average permeability ranging from about 50 cc/cm²/min. to about 5000 cc/cm²/min. on at least one of an inside or outside surface of the stent; adhering at least a portion of the graft to the stent; and forming a membrane having an average permeability ranging from about 0 cc/cm²/min. to about 100 cc/cm²/min. on at least a portion of the stent. The method of making a stent-graft-membrane may further include prior to the step of adhering, applying a thermoplastic adhesive, curable adhesive, or biabsorbable polymer adhesive to a surface of the stent or to a surface of the graft.

The invention also relates to an implantable endoprosthesis including a first number of elongated members wound helically in a first common direction and crossing a second number of elongated members wound helically in a second common direction. The crossing of the first and second elongated members define an angle and form a generally tubular body having an inside surface, outside surface, ends and a middle portion therebetween. The first and second elongated members are braided in a braid pattern and are configured to be constrainable to a reduced diameter and self-expandable to an increased diameter. The tubular body is adapted to be disposed at a treatment site in at least one of a body vessel or organ having body tissue. A passage extends in a longitudinal direction at least partially through the tubular body. The passage is adapted to at least partially contain a fluid. One or more outside layers are disposed over at least a portion of the outside surface of the tubular body. At least one of the outside layers is a membrane made of a silicone or a polycarbonate urethane material biocompatible

with the body tissue. One or more inside layers are disposed over at least a portion of the inside surface of the tubular body. At least one of the inside layers is a graft made of braided PET material biocompatible with the fluid in the passage. The implantable endoprosthesis is configured such that at least one of the outside layers is substantially impermeable to a fluid and substantially separates a first body fluid located outside the endoprosthesis from a second body fluid located in the passage. A first end portion of the implantable endoprosthesis may be disposed in a portal vein and the other end portion of the implantable endoprosthesis may be disposed in a hepatic vein. A middle portion of the braided implantable endoprosthesis may be disposed in a liver. The first fluid may be bile and the second fluid may be blood.

A preferred use includes placing the stent-graft-membrane through a liver. Transjugular Intrahepatic Portosystemic Shunt (TIPS) is formed by an intrahepatic shunt connection between the portal venous system and the hepatic vein for prophylaxis of variceal bleeding, in the treatment of portal hypertension and its complications. Portal hypertension causes blood flow to be forced backward, causing veins to enlarge, resulting in variceal bleeding. The stent-graft-membrane advantageously acts as a shunt to enable blood to flow through the liver to the hepatic vein. The shunt generally decompresses portal hypertension and allows veins to shrink to normal size, stopping the variceal bleeding.

The invention also relates to a method of using a stent-graft-membrane comprising the steps: identifying a treatment site; determining the tissue, organ or fluid at the treatment site that the inside surface and the outside surface of the stent-graft-membrane are to be associated with; determining one or more materials for the inside and outside surfaces of the stent-graft-membrane that are substantially biocompatible with the tissue, organ or fluid at the treatment site; providing a stent-graft-membrane. The stent-graft-membrane having a first number of elongated members wound helically in a first common direction and crossing a second number of elongated members wound helically in a second common direction. The crossing of the first and second elongated members defining an angle therebetween and forming a generally tubular body having an inside surface, outside surface, ends and a middle portion therebetween. The first and second elongated members are braided in a braid pattern and are configured to be constrainable to a reduced diameter and self-expandable to an increased diameter. The generally tubular body is adapted to be disposed at a treatment site in at least one of a body vessel or organ having body tissue. A passage extends in a longitudinal direction at least partially through the generally tubular body. The passage is adapted or configured to at least partially contain a fluid. One or more outside layers are disposed over or on at least a portion of the outside of the tubular body. An outermost layer of the one or more outside layers is substantially biocompatible with the body tissue. One or more inside layers are disposed over or on at least a portion of the inside of the tubular body. An innermost layer of the one or more inside layers is substantially biocompatible with the fluid in the passage. At least one of the one or more outside layers or the one or more inside layers are substantially impermeable to fluids; inserting the stent-graft-membrane in a delivery device; inserting the delivery device into a body and delivering the stent-graft-membrane and at least a portion of the delivery device to the treatment site; and deploying the stent-graft-membrane into a position at the treatment site.

In the design of an implantable medical device such as a stent-graft-membrane, it is important that each of the com-

ponent materials be biocompatible with the host tissue. Thus, an implantable medical device should accomplish its intended functional purpose in the body, and should generally not cause an unfavorable reaction in the tissue with which it interacts.

Biocompatibility requirements may vary for different components of an implantable device. For example, in the case of an implant which is placed in a blood vessel, the inside surface of the implant must be biocompatible with the blood flowing through the lumen. Also, the outside surface of the implant must be biocompatible with the tissue of the blood vessel.

For example, in the case of a TIPS stent-graft-membrane, the general purpose of the stent-graft-membrane is to maintain a shunt for blood flow between the portal and hepatic veins. Each component in the stent-graft-membrane has a function which contributes to the general purpose of the device. In a TIPS application, the functional requirement of the stent is to mechanically hold the liver tissue open to maintain the shunt lumen. The functional requirement of the outer membrane is to prevent any inter-mixing of the bile, which is produced by the liver, into the blood which is flowing through the shunt. Inter-mixing of bile and blood may cause the blood to form thrombus. The functional requirement of the inside graft is to provide an interface with the blood which advantageously improves the blood biocompatibility of the implant.

The stent, graft, or membrane layers may be substantially individual layers that are at least partially bonded together. Alternatively, the stent-graft-membrane may include a stent embedded in the membrane or the membrane embedded in the stent; the stent embedded in the graft or the graft embedded in the stent; and the membrane embedded in the graft or the graft embedded in the membrane. At least one of the stent, graft, or membrane may be embedded in the other.

Each embodiment of the stent-graft-membrane may include a radiopaque tracer wire to make one or more portions more visible during fluoroscopy. Each embodiment of the stent-graft-membrane may include bare filaments at one or more end portions or middle portions.

Still other objects and advantages of the present invention and methods of construction and use of the same will become readily apparent to those skilled in the art from the following detailed description, wherein only the preferred embodiments are shown and described, simply by way of illustration of the best mode contemplated of carrying out the invention. As will be realized, the invention is capable of other and different embodiments and methods of construction and use, and its several details are capable of modification in various obvious respects, all without departing from the invention. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 illustrates a side view of an embodiment of the stent-graft-membrane having a stent outside layer, graft middle layer, and membrane inside layer;

FIG. 1A illustrates an end view of the stent-graft-membrane of FIG. 1;

FIG. 2 illustrates a side view of an embodiment of the stent-graft-membrane having a stent outside layer, membrane middle layer, and graft inside layer;

FIG. 2A illustrates an end view of the stent-graft-membrane of FIG. 2;

FIG. 3 illustrates a side view of an embodiment of the stent-graft-membrane having a graft outside layer, stent middle layer, and membrane inside layer;

FIG. 3A illustrates an end view of the stent-graft-membrane of FIG. 3;

FIG. 4 illustrates a side view of an embodiment of the stent-graft-membrane having a graft outside layer, membrane middle layer, and stent inside layer;

FIG. 4A illustrates an end view of the stent-graft-membrane of FIG. 4;

FIG. 5 illustrates a side view of an embodiment of the stent-graft-membrane having a membrane outside layer, graft middle layer, and stent inside layer;

FIG. 5A illustrates an end view of the stent-graft-membrane of FIG. 5;

FIG. 6 illustrates a side view of an embodiment of the stent-graft-membrane having a membrane outside layer, stent middle layer, and graft inside layer;

FIG. 6A illustrates an end view of the stent-graft-membrane of FIG. 6;

FIGS. 7-8 illustrate end views of two embodiments of the stent-graft-membrane;

FIG. 9 illustrates a side view of an embodiment of the stent-graft-membrane with an exposed middle portion;

FIG. 10 illustrates a side view of an embodiment of a fully covered stent-graft-membrane;

FIG. 11 illustrates a side view of an embodiment of the stent-graft-membrane with one exposed end portion;

FIG. 12 illustrates a side view of an embodiment of the stent-graft-membrane with two exposed end portions;

FIG. 13 illustrates a TIPS treatment site; and

FIG. 14 illustrates a stent-graft-membrane at a TIPS treatment site.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Reference is made to FIGS. 1-6 showing various embodiments of a stent-graft-membrane 20 with a radiopaque tracer wire 21.

FIG. 1 illustrates an embodiment of the stent-graft-membrane 20 with a stent layer 22 located on the outside, a graft layer 26 located in the middle, and a membrane layer 30 located on the inside. FIG. 1A illustrates an end view of the stent-graft-membrane 20 in FIG. 1.

FIG. 2 illustrates an embodiment of the stent-graft-membrane 20 having a stent layer 22 located on the outside, a membrane layer 30 located in the middle, and a graft layer 26 located on the inside. FIG. 2A illustrates an end view of the stent-graft-membrane 20 of FIG. 2.

FIG. 3 illustrates an embodiment of the stent-graft-membrane 20 having a graft layer 26 located on the outside, a stent layer 22 located in the middle, and a membrane layer 30 located on the inside. FIG. 3A illustrates an end view of the stent-graft-membrane 20 of FIG. 3.

FIG. 4 illustrates an embodiment of the stent-graft-membrane 20 having a graft layer 26 located on the outside, a membrane layer 30 located in the middle, and a stent layer 22 located on the inside. FIG. 4A illustrates an end view of the stent-graft-membrane 20 of FIG. 4.

FIG. 5 illustrates an embodiment of the stent-graft-membrane 20 having a membrane layer 30 located on the outside, a graft layer 26 located in the middle, and a stent layer 22 located on the inside. FIG. 5A illustrates an end view of the stent-graft-membrane 20 of FIG. 5.

FIG. 6 illustrates an embodiment of the stent-graft-membrane 20 having a membrane layer 30 located on the outside, a stent layer 22 located in the middle, and a graft layer 26 located on the inside. FIG. 6A illustrates an end view of the stent-graft-membrane 20 of FIG. 6.

General descriptions of the stent 22, graft 26 and membrane 30 include:

A. Stent

The stent is a tubular mesh including interbraided helically-wound filaments. The tubular mesh is capable of a reduction in diameter with a corresponding increase in length. The reduction in diameter facilitates the delivery of the endoprosthesis to the implant site by a deployment catheter. The filaments may include metal having a sufficiently high modulus of elasticity to provide elasticity to the braided structure. The metal structure is age hardened to augment the resiliency of the stent. This results in a self-expanding structure which opens to an expanded diameter when released from a constrained state.

Stent filaments may be made of implantable grade medical stainless steels, Elgiloy®, Conichrome, Phynox, MP35N, nickel/titanium alloys, Nitinol, cobalt-based alloys, CoCrMo, Titanium alloys, titanium-zirconium-niobium alloys, titanium-aluminum-vanadium alloy known as TI-6Al-4V, drawn filled tube (DFT), platinum, tungsten, tantalum, or combinations thereof.

Stent filaments may also be made of polymers, bioabsorbable polymers, PET, polypropylene, PEEK, HDPE, polysulfone, acetyl, PTFE, FEP, and polyurethane, or combinations thereof.

Stent filaments may also be made of poly (alpha-hydroxy acid), PGA, PLA, PLLA, PDLA, polycaprolactone, polydioxanone, polygluconate, polylactic acid-polyethylene oxide copolymers, modified cellulose, collagen, poly (hydroxybutyrate), polyanhidride, polyphosphoester, poly (amino acids), or combinations thereof.

Average diameters of the filaments may range from about 0.002 inches to about 0.015 inches.

B. Graft

The graft is designed to be compatible with the body tissue or the fluid that it contacts. For example, if the graft is placed on the outside of a stent and is intended for placement in an airway, the graft is made of a material that is compatible with the tissue on the inside of the airway. If the graft is placed on the inside of a stent and is intended for placement in a blood vessel, the graft is made of a material that is compatible with blood.

A preferred embodiment of the graft includes a tubular mesh of interbraided polyethylene terephthalate (PET) yarns. This graft includes two sets of textile strands, helically wrapped in opposite directions around a mandrel in an intertwining pattern to produce a graft which behaves according to approximately the same axial lengthening/diametrical reduction relationship as the stent. Other possible graft structures may include woven or knitted textile grafts and spun-filament grafts. The graft generally has a lower permeability than the stent.

Textile strands preferably are multifilament yarns, although they can be monofilaments. The textile strands range from about 10 denier to 400 denier. Individual filaments of the multifilament yarns can range from about 0.25 to about 10 denier. Permeability ranges from about 50 cc/cm²/min. to about 5000 cc/cm²/min. at about 120 mmHg differential pressure. The graft layer may be made of spun polycarbonate urethane to create a tubular structure. The

graft may have an average wall thickness between about 0.001 and about 0.010 inch.

Graft materials may include PET such as Dacron, ePTFE, polyurethane, polycarbonate urethane, polypropylene, polyethylene such as Spectra, HDPE, silicone, PTFE, and polyolefins.

C. Membrane

The membrane is designed to limit permeability. Permeability is defined as the ability of fluids to flow through the wall of the stent-graft-membrane. A purpose of the membrane is to further restrict the flow of fluids through the wall of a stent or stent-graft. The membrane can be made by a number of different techniques and a number of different materials. Permeability of the membrane ranges from about 0 cc/cm²/min. to about 100 cc/cm²/min. at 120 mmHg differential pressure. Membrane materials may include siloxane polymers, polyurethane polymers, polycarbonate urethanes, PTFE or ePTFE.

A membrane may be formed on a stent or stent-graft by dipping the stent or stent-graft into a solution including a polymer with a solvent. In this case, the membrane may become embedded in the stent or stent-graft and is generally not a discrete layer. The stent or stent-graft is then removed from the solution, forming a membrane on the stent or stent-graft. The solvent is evaporated from the membrane, and the polymer is cured, if a curable polymer such as silicone is used. The membrane layer may have a thickness between about 0.001 and about 0.010 inch.

A membrane may also be formed by impregnating a porous graft with a polymer. The polymer becomes integrated in the graft interstices, resulting in a graft-membrane which has substantially lower permeability than the graft starting material.

A membrane may also be formed by providing a stent-graft having a stent on the inside layer and a braided PET graft on the outside layer. The stent-graft is placed over a mandrel which has an outer diameter similar to the inner diameter of the stent-graft. The ends of the mandrel are affixed in a machine which rotates the stent-graft and mandrel about a central axis. Using an airbrush or similar spraying apparatus, the stent-graft is sprayed with a solution of silicone in a volatile solvent such as tetrahydrofuran. A volume of approximately 10 cc of silicone solution is sprayed intermittently over a period of approximately fifteen minutes onto the stent-graft. The sprayed stent-graft-membrane and mandrel are placed in an oven at 150° C. for a period of 30 minutes to cure the silicone polymer. After the stent-graft-membrane is formed, the stent, graft and membrane composite is substantially impermeable. An additional graft layer may be bonded on the inside or outside of the stent-graft-membrane depending on biocompatibility needs. For example, if a silicone has embedded in the graft, the silicone may extend to the inside surface where blood flow occurs. In that case, it may be desirable to add a PET braided graft on the inside for biocompatibility purposes.

D. Methods For Applying A Membrane To A Stent

1. Dip coating: Dip the stent or stent-graft into polymer dissolved in solvent to coat the stent, then evaporate the solvent (and cure the polymer, if applicable) to form a film.

2. Spray coating: Spray a polymer in solution on to the inside or outside surface of the stent or stent-graft. Then, evaporate the solvent (and curing the polymer, if applicable) to form a film.

3. Apply a polymeric film or tube to the inside and/or outside surface of the stent or stent-graft. Then, fuse the

membrane to the stent or stent-graft by use of adhesive, solvent bonding, or by thermal and/or pressure bonding.

EXAMPLE 1

5 A stent-graft-membrane 20 was made by spraying silicone on a stent-graft. A 10 mm diameter and 50 mm length stent-graft comprising an Elgiloy stent and braided PET graft were bonded together with polycarbonate urethane and placed over a 10 mm diameter mandrel that was first sprayed with a TFE release agent. The mandrel and the stent-graft were placed on a rotational fixture and the motor was turned on to rotate the stent-graft. The stent-graft was coated with a volume of approximately 10 cc of a 6% solid silicone solution. The silicone solution was applied with an airbrush from a distance of approximately 8–10 cm. The solution was applied intermittently over the course of approximately 15 minutes to allow the THF and Xylene solvents to evaporate from the stent-graft surface as it was sprayed in order to prevent the graft from becoming too wet. After the silicone was applied, the mandrel and stent-graft-membrane were placed in an oven at 150° C. for a period of 30 minutes to cure the silicone polymer. After 30 minutes, the stent-graft-membrane was removed from the oven and allowed to cool.

20 Alternative methods of making the stent-graft-membrane 20 in Example 1 can include: spraying a stent and graft assembly that has not been bonded together with a polymer in solution; spraying the stent-graft with polycarbonate urethane; using a non-coated graft on the inside of stent; or using a mandrel coated with PTFE.

25 In a preferred embodiment of the stent-graft-membrane 20, a first number of elongated members 22a are wound in a helical pattern in a first common direction and cross a second number of elongated members 22b wound in a helical pattern in a second common direction. As shown in FIG. 5, the crossing point 23 of the first and second elongated members 22a, 22b define an angle θ. The elongated members 22a, 22b form a stent 20 having an inside surface, outside surface, ends and a middle portion. The elongated members 22a, 22b are braided in a braid pattern and are constrainable to a reduced diameter and are self-expandable to an increased diameter. An outside layer such as graft layer 26 or membrane layer 30 is disposed over or on at least a portion of the outside surface of the stent 22. The outermost layer is biocompatible with the body tissue. An inside layer such as graft layer 26 or membrane layer 30 is disposed over or on at least a portion of the inside surface of the stent 22. The innermost layer is biocompatible with the fluid in the passage 38. The membrane layer 30 that is located outside or inside the stent 22 is substantially impermeable to fluids. Average permeability of a membrane layer 30 ranges from about 0 cc/cm²/min. to about 100 cc/cm²/min. at 120 mmHg differential pressure and the average permeability of a graft layer 26 ranges from about 50 cc/cm²/min. to about 5000 cc/cm²/min. at 120 mmHg differential pressure. The membrane layer 30 is made of silicone or polycarbonate urethane and the graft layer 26 is made of braided PET. A passage 38 extends in a longitudinal direction at least partially through the stent-graft-membrane 20. The passage 38 is for channeling fluid and for providing a flow direction for the fluid in a vessel or organ.

30 Another preferred embodiment of the stent-graft-membrane 20 includes a first set of filaments 22a which extend in a configuration along a center line and have a first common direction of winding. A second set of filaments 22b extend in a configuration along a center line and have a second common direction of winding. The first and second

filaments 22a, 22b form a stent 22. A membrane layer 30 with a first average permeability is disposed on the inside or the outside of the stent 22. A graft layer 26 with a second average permeability is disposed over or on the inside or the outside of the stent 22. The first and second set of filaments 22a, 22b, membrane layers 30, and graft layers 26 form a self expanding structure having an inside layer, outside layer, and a lumen 38. The membrane layer 30 may be disposed between the graft 26 and the stent 22. The graft layers 26 may be disposed between the membrane 30 and the stent 22. The stent 22 may be outside or inside the graft 26 and membrane 30. The layers 22, 26, 30 may be bonded by an adhesive. The inside layer is biocompatible with a fluid flow through the body lumen and the outside layer is biocompatible with body tissue. The membrane layer 30 has an average permeability ranging from about 0 cc/cm²/min. to about 100 cc/cm²/min. at 120 mmHg differential pressure and the graft layer 26 has an average permeability ranging from about 50 cc/cm²/min. to about 5000 cc/cm²/min. at 120 mmHg differential pressure. The graft layer 26 may include a plurality of interwoven fibers, mono-filaments, multi-filaments, or yarns. The graft layer 26 may include polyethylene terephthalate (PET), expanded polytetrafluoroethylene (ePTFE), polycarbonate urethane (PCU), polyurethane (PU), or combinations thereof. The membrane layer 30 may include siloxane polymers, polyurethane polymers, polycarbonate urethanes, PTFE, ePTFE, or combinations thereof. The membrane layers 30 may be a film, sheet, or tube. The stent-graft-membrane 20 substantially excludes a first fluid located outside the stent-graft-membrane 20 from reaching a second fluid located in the lumen 38.

Another preferred embodiment of the stent-graft-membrane includes one or more outside layers disposed over or on the outside of the stent 22. The outside layer is a membrane 30 made of a silicone or a polycarbonate urethane material that is biocompatible with the body tissue. One or more inside layers are disposed over or on the inside of the stent 22. The inside layer is a graft 26 made of braided PET material biocompatible with the fluid in the passage 38. The graft 26 may be braided, spun or spray-cast. The outside layers are substantially impermeable to a fluid and substantially separate a first body fluid located outside the stent-graft-membrane 20 from a second body fluid located in the passage 38.

FIG. 7 illustrates an end view of a stent-graft-membrane 20 in which the inside layer is a graft layer 26 made of braided PET, the middle layer is a braided stent 22, and the outer layer is a membrane layer 30 made of silicone. The composite layers include three-layers 22, 26, 30 which may be bonded together under heat and pressure so that the membrane layer 30 conforms to the profile of the stent layer 22 and graft layer 26 as shown.

FIG. 8 illustrates a stent-graft-membrane 20. The inside layer is a graft layer 26 made of braided PET. The middle layer is a braided stent 22. The outside layer is a graft layer 26 made of braided PET which has been impregnated with 55 silicone to create a substantially impermeable graft/membrane layer 26,30 as described in Example 1.

Various portions of the stent-graft-membrane 20 may be covered by the graft 26 or membrane 30. For example, FIG. 9 illustrates a stent-graft-membrane 20 with an exposed 60 middle portion 20b. FIG. 10 illustrates a fully covered stent-graft-membrane 20. FIG. 11 illustrates a stent-graft-membrane 20 with one exposed end portion 20a. FIG. 12 illustrates a stent-graft-membrane 20 with two exposed end portions 20a, 20c.

FIG. 13 illustrates a TIPS treatment site 50. FIG. 14 illustrates a stent-graft-membrane 20 disposed at a TIPS

treatment site 50. The stent-graft-membrane 20 may be used for creation or revision of a transjugular intrahepatic porto-systemic shunt (TIPS). The stent-graft-membrane 20 substantially separates a first fluid such as bile located outside the stent-graft-membrane 20 from a second fluid such as blood located and channeled in the passage 38. One end portion of the stent-graft-membrane 20 is disposed in a portal vein, a middle portion of the stent-graft-membrane 20 is disposed in a liver, and the other end portion is disposed in a hepatic vein.

A TIPS treatment method includes puncturing the right internal jugular vein; advancing a wire into the IVC followed by a 40 cm, 9-10 F sheath with a hemostatic valve; catheterizing the hepatic vein; using a stiff wire to introduce 15 the needle set; positioning the needle in the hepatic vein and retracting the sheath to reveal the needle tip; advancing the needle through the liver and puncturing the portal vein; injecting contrast to identify the vascular structure; advancing a guidewire through the needle; the wire should enter the 20 portal vein; removing the needle; introducing a catheter; measuring portal pressure; performing a portal venogram; exchanging the catheter for a balloon; dilating the parenchymal tract; advancing the vascular sheath into the tract and removing the balloon; introducing the stent-graft-membrane into the portal vein; positioning and deploying the 25 stent-graft-membrane; exchanging the delivery sheath for a 5 Fr, 8 mm balloon; expanding the stent-graft-membrane; repeating the venogram and pressure measurement; and dilating if necessary. The sizes of the equipment 30 and stent-graft-membrane used in the TIPS procedure may vary.

The above described embodiments of the invention are merely descriptive of its principles and are not to be considered limiting. Further modifications of the invention 35 herein disclosed will occur to those skilled in the respective arts and all such modifications are deemed to be within the scope of the invention as defined by the following claims.

I claim:

1. A body compatible endoprosthesis, including:
a tubular body including a tubular structural mesh layer;
the tubular body further including a graft layer formed of
a graft material and having a graft layer surface that
forms an inside surface of the tubular body and defines
a fluid passage in the tubular body, said graft layer
having a first average permeability within a range from
about 50 cc/cm²/min. to about 5,000 cc/cm²/min. at
120 mm Hg and being biocompatible with a first fluid
contained in the fluid passage; and
the tubular body further including a membrane layer
formed of a membrane material, substantially sur-
rounding the graft layer, and having a second average
permeability less than the first average permeability.
2. The endoprosthesis of claim 1 wherein:
the tubular structural mesh layer comprises first and
second sets of filaments helically wound in respective
first and second different common directions.
3. The endoprosthesis of claim 2 wherein:
the tubular body is radially reducible to a reduced
diameter, and enlargable to an increased diameter.
4. The endoprosthesis of claim 3 wherein:
the tubular body is constrainable to a reduced diameter
and self-expandable to an increased diameter.
5. The endoprosthesis of claim 1 wherein:
the tubular body is adapted for deployment at a treatment
site along body tissue, the membrane layer has a
membrane layer surface that forms an outside surface

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- of the tubular body adapted to contact the body tissue upon said deployment, and the membrane layer is biocompatible with said body tissue.
6. The endoprosthesis of claim 1 wherein:
said second average permeability of the membrane layer is at most about 100 cc/cm²/min. at 120 mm/Hg. 5
7. The endoprosthesis of claim 1 wherein:
said membrane material comprises at least one material from the group consisting of: silicone elastomers, polyurethane polymers, polycarbonate urethanes, polytetrafluoroethylene (PTFE), and ePTFE. 10
8. The endoprosthesis of claim 7 wherein:
said membrane material is a silicone elastomer.
9. The endoprosthesis of claim 1 wherein:
said graft material comprises at least one of the materials selected from the group consisting of: polyethylene terephthalate (PET), polytetrafluoroethylene (PTFE), expanded polytetrafluoroethylene (ePTFE), polycarbonate urethane, polyurethane, polypropylene, 15 polyethylene, silicone, and polyolefins. 20
10. The endoprosthesis of claim 9 wherein:
the graft material is polyethylene terephthalate (PET).
11. The endoprosthesis of claim 1 wherein:
the membrane layer is configured to substantially isolate 25 the first fluid contained in the fluid passage from a second fluid located outside the tubular body.
12. The endoprosthesis of claim 11 wherein:
the first fluid comprises blood, and the second fluid comprises bile. 30
13. The endoprosthesis of claim 12 wherein:
said tubular body is adapted to be deployed at a transjugular intrahepatic portal systemic shunt (TIPS) treatment site.
14. The endoprosthesis of claim 1 wherein:
the membrane layer is disposed between the graft layer 35 and the structural mesh layer.
15. The endoprosthesis of claim 1 wherein:
the graft layer is disposed between the membrane layer and the structural mesh layer. 40
16. The endoprosthesis of claim 1 wherein:
the structural mesh layer is disposed between the membrane layer and the graft layer.
17. The endoprosthesis of claim 1 wherein:
said membrane layer is formed by coating the structural 45 mesh layer with the membrane material.
18. The endoprosthesis of claim 1 further including:
a porous layer formed of a graft material and disposed adjacent the structural mesh layer; and
wherein the membrane layer consists essentially of a 50 coating of the membrane material applied to the structural mesh layer and to the porous layer.
19. The endoprosthesis of claim 1 wherein:
the membrane layer consists essentially of a porous layer 55 formed of a graft material and impregnated with the membrane material.
20. An implantable endoprosthesis including:
a tubular mesh structure;
a tubular first graft layer surrounded by the mesh structure; 60
a tubular second graft layer surrounding the first graft layer; and
a membrane material applied to a selected one of the first and second graft layers, thus to provide in the selected 65 graft layer a first average permeability less than a second average permeability of the other graft layer.

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21. The endoprosthesis of claim 20 wherein:
said selected graft layer is the second graft layer.
22. The endoprosthesis of claim 20 wherein:
the selected graft layer has a permeability of at most about 100 cc/cm²/min. at 120 mm/Hg., and said other graft layer has an average permeability ranging from about 50 to about 5000 cc/cm²/min. at 120 mm. Hg.
23. The endoprosthesis of claim 20 wherein:
the second graft layer further surrounds the mesh structure.
24. The endoprosthesis of claim 20 wherein:
the mesh structure surrounds the first graft layer and the second graft layer.
25. The endoprosthesis of claim 20 wherein:
the membrane material forms a coating on the selected graft layer.
26. The endoprosthesis of claim 20 wherein:
the membrane material impregnates the selected graft layer.
27. The endoprosthesis of claim 20 wherein:
the selected graft layer is disposed adjacent the mesh structure, and the membrane material coats the selected graft layer and the structural mesh layer, average permeability, and is adapted for isolating the first fluid in the passage from a second fluid located outside the passage.
28. An implantable endoprosthesis comprising:
a tubular mesh structure having a longitudinal passage extending therethrough;
a membrane consisting essentially of a porous layer formed of a graft material and coated with a membrane material disposed on at least a portion of the outside of the tubular mesh structure;
a graft layer disposed on at least a portion of the inside of the tubular mesh structure;
wherein the graft layer has a first average permeability and is adapted for containing a first fluid in the passage, and the membrane has a second average permeability less than the first average permeability, and is adapted for isolating the first fluid in the passage from a second fluid located outside the passage.
29. The endoprosthesis of claim 28 wherein:
the first permeability ranges from about 50 to about 5,000 cc/cm²/min. at 120 mm/Hg., and the second average permeability is at most about 100 cc/cm²/min. at 120 mm. Hg.
30. The endoprosthesis of claim 28 wherein:
the first fluid consists essentially of blood, and the second fluid consists essentially of bile.
31. The endoprosthesis of claim 28 wherein:
the membrane material further is applied to the tubular mesh structure.
32. The endoprosthesis of claim 20 wherein:
said mesh structure comprises first and second sets of filaments wound helically in respective and different first and second directions, crossing one another to form multiple crossing points.
33. The endoprosthesis of claim 32 wherein:
the mesh structure is constrainable to a reduced diameter and self-expandable to an increased diameter.
34. A process for making an implantable endoprosthesis, including:
providing a tubular mesh structure;
forming a graft layer of a graft material with a first average permeability, and disposing the graft layer along an inside surface of the tubular mesh structure; and

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forming a membrane layer by disposing a porous layer of a graft material along an outside surface of the tubular mesh structure and coating the porous layer with a membrane material, said membrane layer having a second average permeability less than the first average permeability of the graft layer.

35. The process of claim 34 wherein:

the forming of the membrane layer further comprises coating the mesh structure with the membrane material.

36. A body compatible endoprosthesis, including:

a tubular body including a tubular structural mesh layer; the tubular body further including a graft layer formed of a graft material and having a graft layer surface that forms an inside surface of the tubular body and defines a fluid passage in the tubular body, said graft layer having a first average permeability and being biocompatible with a first fluid contained in the fluid passage; and

the tubular body further including a membrane layer formed of a membrane material, substantially surrounding the graft layer, and having a second average permeability less than the first average permeability of at most about 100 cc/cm²/min. at 120 mm Hg.

37. The endoprosthesis of claim 36 wherein:

the tubular structural mesh layer comprises first and second sets of filaments helically wound in respective first and second different common directions.

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38. The endoprosthesis of claim 36 wherein: the membrane layer is deposited between the graft layer and the structural mesh layer.

39. The endoprosthesis of claim 36 wherein: the graft layer is disposed between the membrane layer and the structural mesh layer.

40. The endoprosthesis of claim 36 wherein: the structural mesh layer is disposed between the membrane layer and the graft layer.

41. The endoprosthesis of claim 36 wherein: the membrane layer is formed by coating the structural mesh layer with the membrane material.

42. The endoprosthesis of claim 36 further including: a porous layer formed of a graft material disposed adjacent the structural mesh layer, wherein the membrane layer consists essentially of a coating of the membrane material applied to the structural mesh layer and to the porous layer.

43. The endoprosthesis of claim 20 wherein: the mesh structure comprises first and second sets of filaments wound helically in respective first and second different directions, crossing one another to form multiple crossing points.

44. The endoprosthesis of claim 43 wherein: the mesh structure is constrainable to a reduced diameter and self-expandable to an increased diameter.

* * * * *



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United States Patent [19]

Karwoski et al.

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[45] Date of Patent: Mar. 28, 2000

[54] PROSTHESIS WITH IN-WALL MODULATION

[75] Inventors: Theodore Karwoski, Hudson; Paul Martakos, Pelham, both of N.H.; Peter Gingras, Bedford, Mass.; Steve A. Herweck, Nashua; Tom Swanick, Mont Vernon, both of N.H.

[73] Assignee: Atrium Medical Corporation, Hudson, N.H.

[21] Appl. No.: 09/105,736

[22] Filed: Jun. 26, 1998

Related U.S. Application Data

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[51] Int. Cl.⁷ B32B 31/00

[52] U.S. Cl. 156/47; 156/50

[58] Field of Search 156/60, 50, 47

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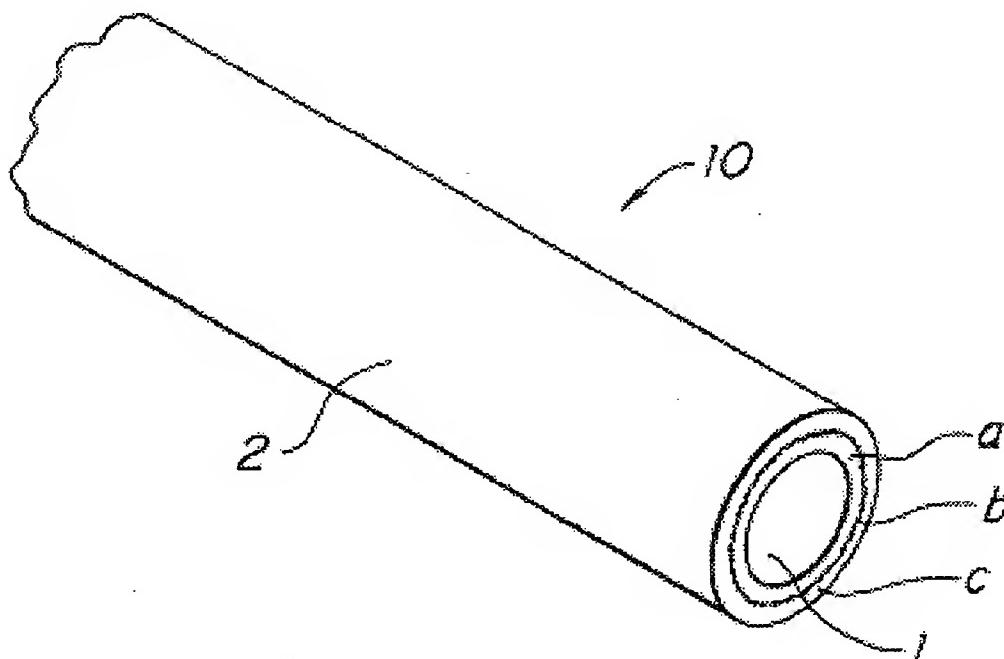
Primary Examiner—Francis J. Lorin
Attorney, Agent, or Firm—Lahive & Cockfield, LLP

[57]

ABSTRACT

The wall of a prosthesis has a region which modulates communication through the porosity of the wall. The prosthesis is unitary, but may be assembled in successive bodies which are coalesced, so that the porous microstructure changes distinctly at stages through the thickness dimension of the wall. One embodiment is formed entirely of fluoropolymer, and has at least one surface adapted to support tissue regeneration and ingrowth. The modulation region is a stratum of high water entry pressure that reduces pulsatile hydraulic pressure transmission, or locally alters fluid-born-distribution of biological material through the wall and allows more natural gradients for tissue regeneration and growth in the outer region of the wall.

28 Claims, 5 Drawing Sheets



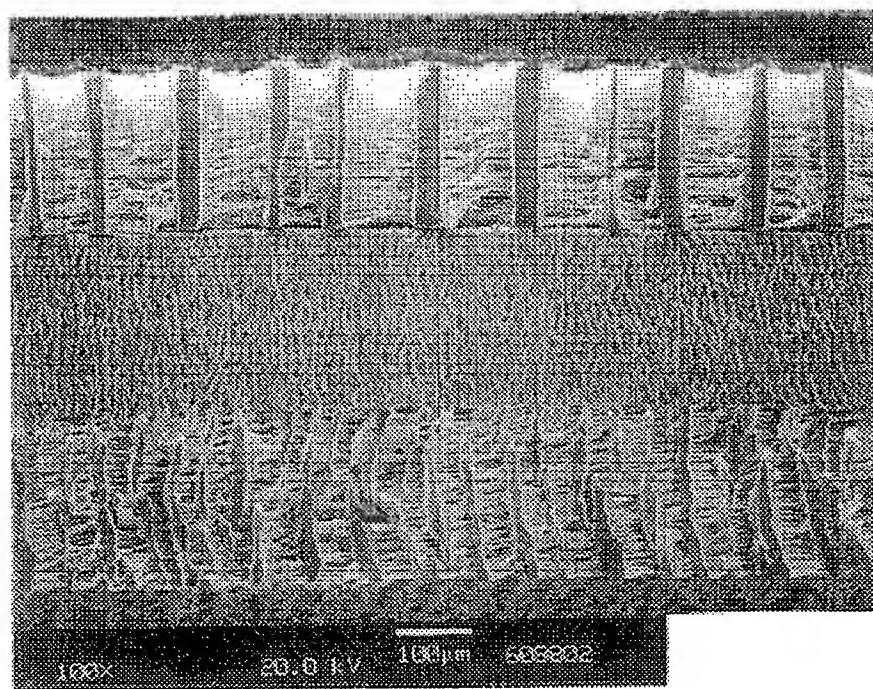


FIG. 1

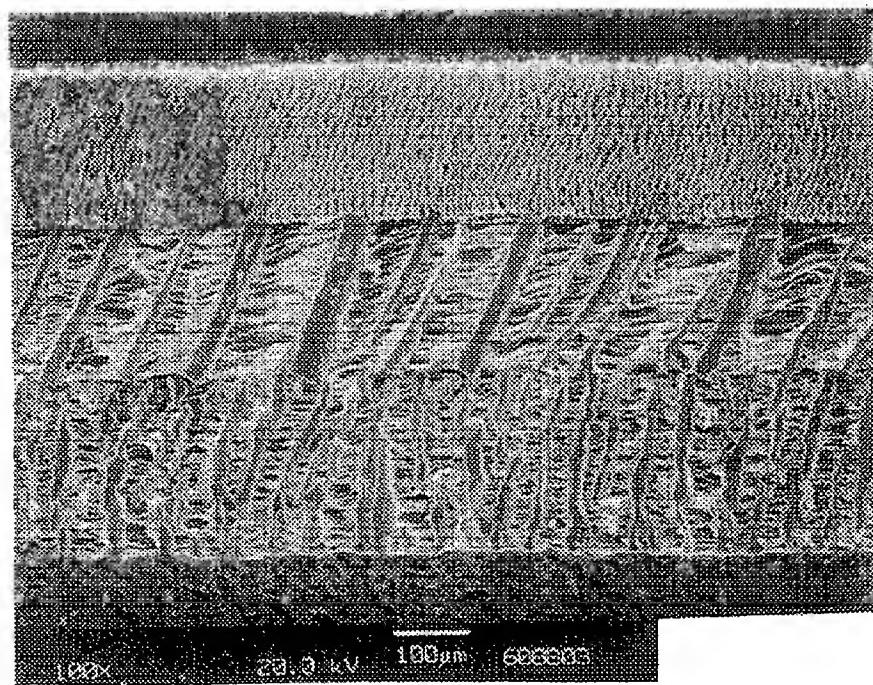


FIG. 2

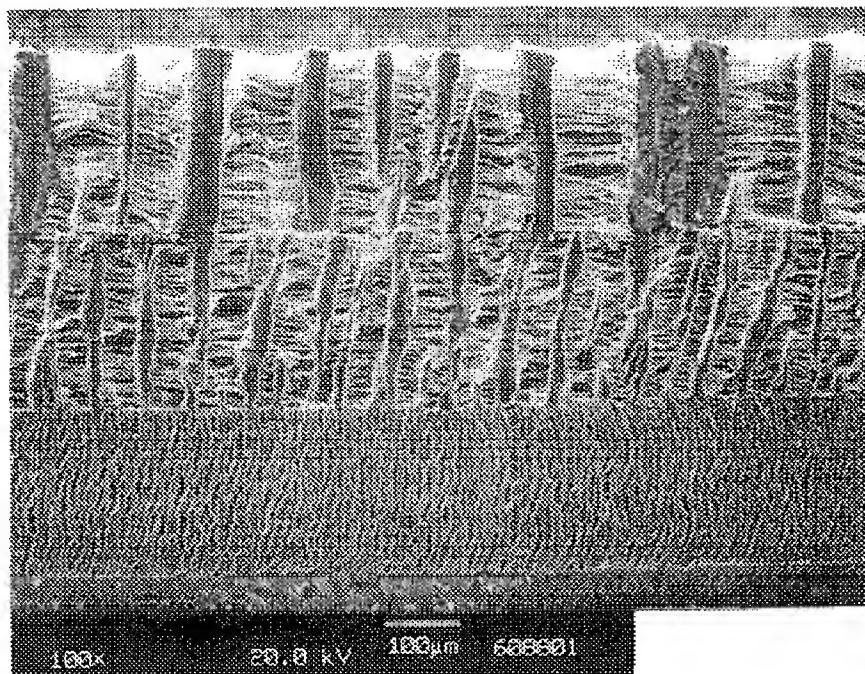


FIG. 3

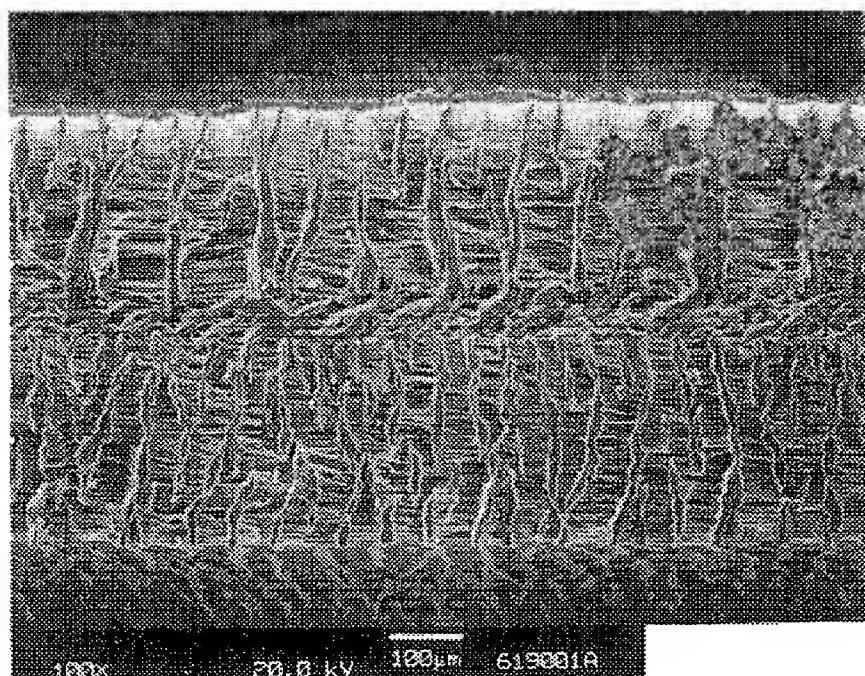


FIG. 4

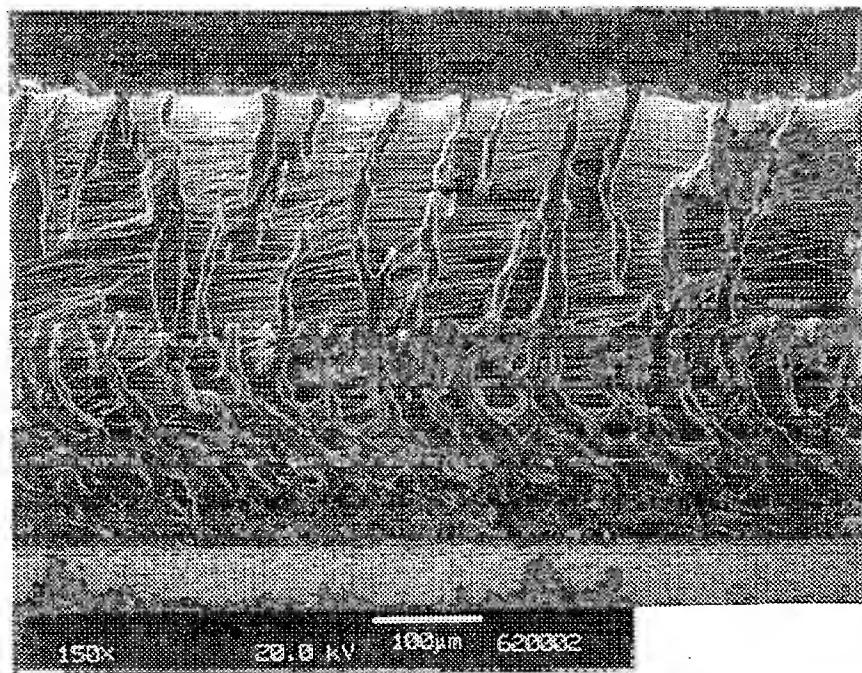


FIG. 5

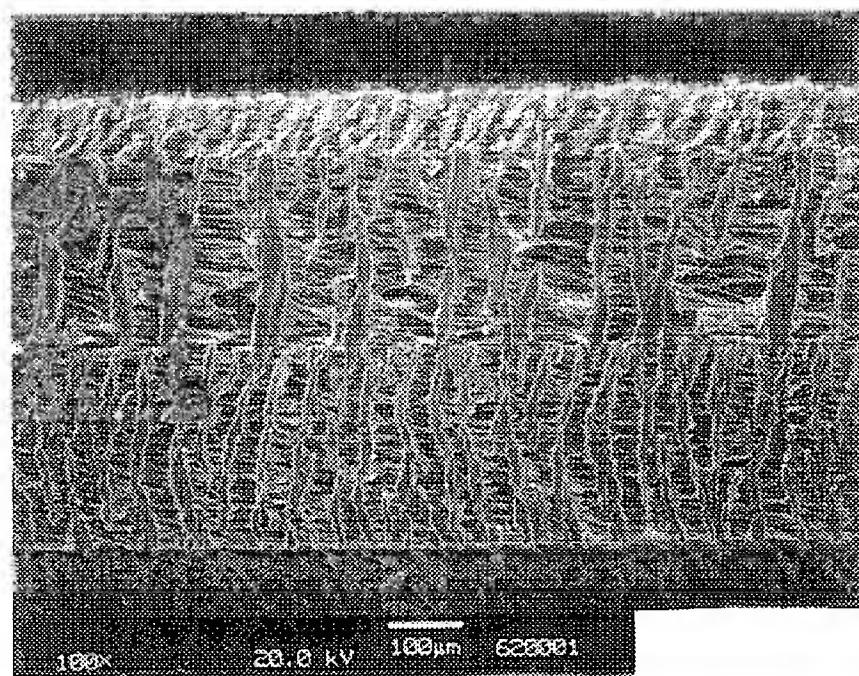


FIG. 6

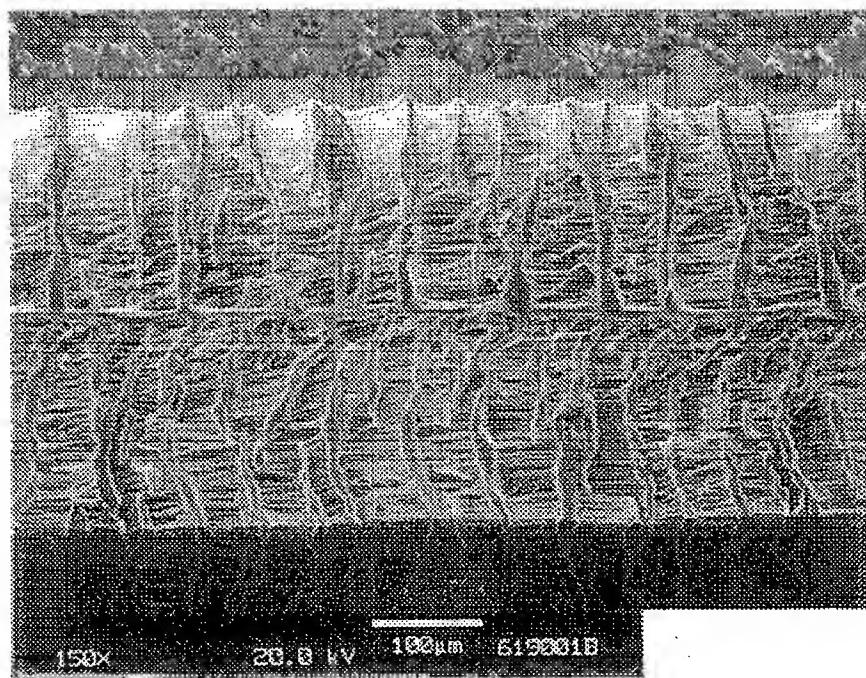


FIG. 7

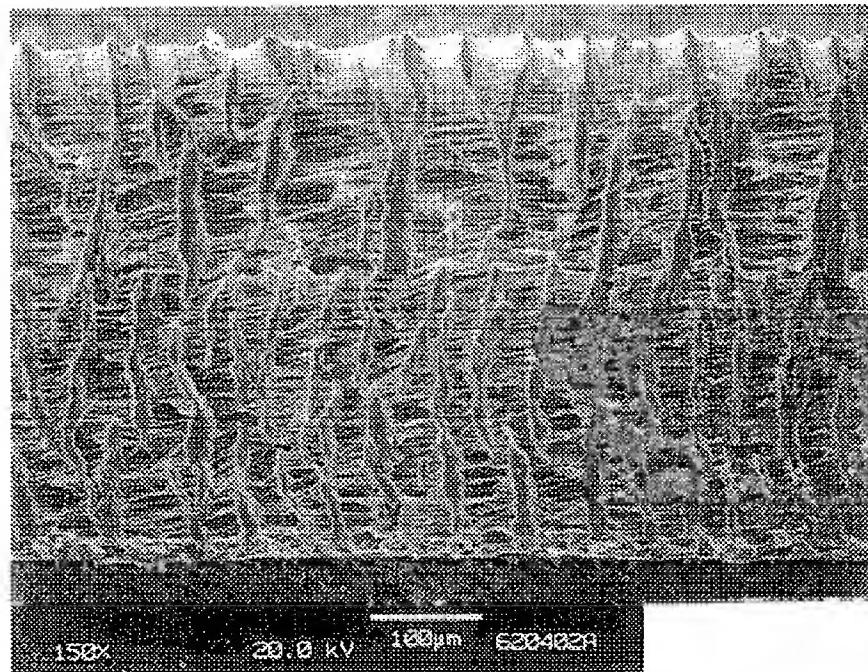


FIG. 8

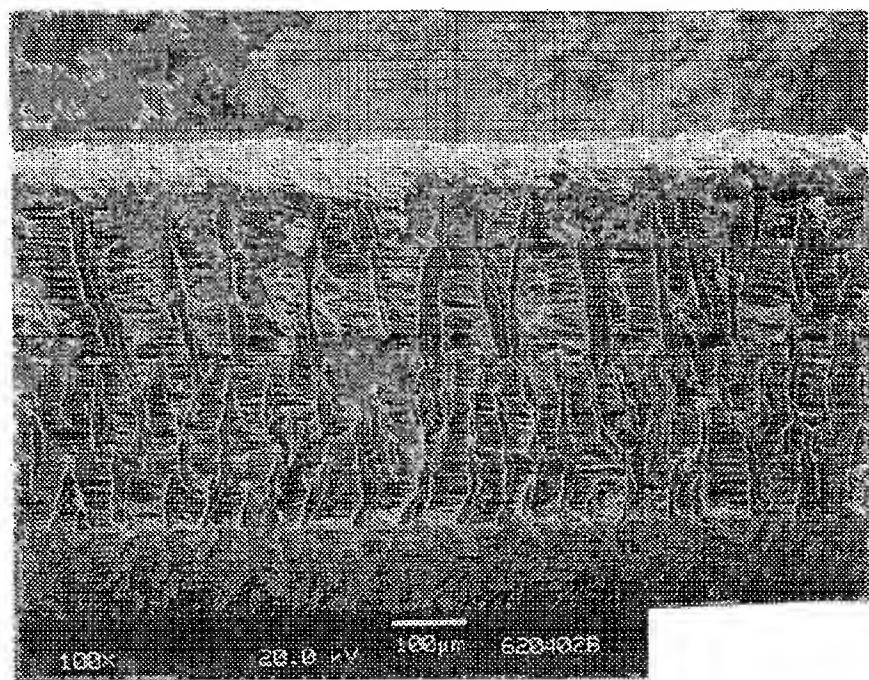


FIG. 9

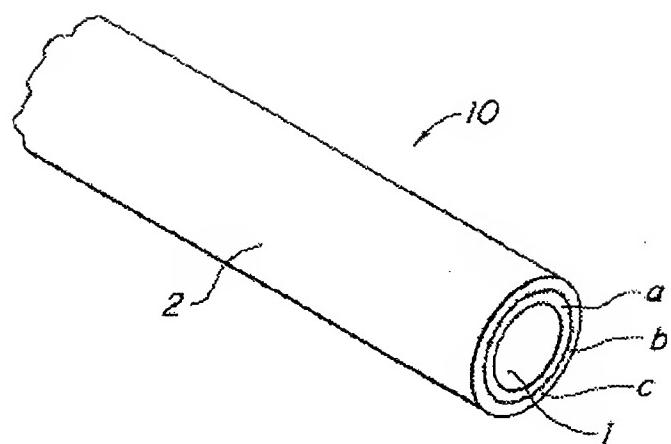


FIG. 10

PROSTHESIS WITH IN-WALL MODULATION

REFERENCE TO RELATED PATENTS AND PATENT APPLICATIONS

This application is a divisional of allowed U.S. application Ser. No. 08/760,115, filed Dec. 3, 1996, now U.S. Pat. No. 5,824,050, and incorporated herein by reference.

This application relates to the commonly owned United States patent applications having the following titles and patent application numbers: VASCULAR ENDOPROSTHESIS AND METHOD, patent application Ser. No. 08/759,861; MULTI-STAGE PROSTHESIS, patent application Ser. No. 08/760,113; EXPANDABLE SHIELDED VESSEL SUPPORT, patent application Ser. No. 08/759,877. It also relates to applicants' earlier U.S. Pat. No. 5,433,909 and No. 5,474,824. The foregoing patents describe methods of making extruded PTFE material having large oriented nodes, uniaxially oriented fibrils and a pore structure of oriented channels that differs at different surfaces, or that varies along the thickness dimension. The aforesaid patent applications each describe constructions or methods of use for prostheses, which are further useful in the embodiments and applications of the present invention. Each of the aforementioned United States patents and patent applications is hereby incorporated by reference herein in its entirety.

BACKGROUND

This invention relates to a lamellate polytetrafluoroethylene material that can be formed into an implant where there is an improvement in the surgical handling accompanied with enhanced healing properties due to the novel arrangement of variable porosity regions of polytetrafluoroethylene. This invention relates to materials utilized in the production of devices for in vivo implantation, such as heart valve leaflets, sutures, vascular access devices or any related products, but more particularly relates to vascular grafts, for example, to porous polytetrafluoroethylene prostheses intended for placement or implantation to supplement or replace a segment of a natural, biological blood vessel. It also relates to patches or supports for tissue repair or reinforcement. For simplicity of exposition below, the invention will be discussed solely with relation to an implantable vascular graft, or a liner for a vessel which might, for example, be delivered intraluminally.

Reference is made to commonly-owned U.S. Pat. Nos. 5,433,909 and 5,474,824 which disclose a method and a product made thereby which is an extruded tube of polytetrafluoroethylene having a tailored porosity. The tube is made by extrusion, of a preform having differently-prepared PTFE paste at two or more levels along its radial section, followed by stretching and generally also sintering so as to achieve the desired strength and pore structure in the final product. As described in those patents and elsewhere, porosity may be tailored to achieve certain desirable properties in the structure of nodes and fibrils that affect permeability and various forms of tissue compatibility, such as the promotion or prevention of tissue growth. In particular, the above patents describe a method of fabricating tubes of PTFE material having good mechanical strength, together with a combination of other features including one or more of a large reticulated node structure which enhances tissue growth, a small pore structure which limits weeping of the graft, and different porosities through the thickness portion of the tube wall to achieve desired properties at both surfaces. The

aforesaid commonly-owned patents also describe a method of obtaining these properties in a single PTFE tube in which a property such as lubrication level has been consciously made non-uniform.

Other approaches to extruding a porous PTFE tube have involved stacking two preforms of different PTFE materials, or PTFE and a dissimilar material, together and extruding a layered structure.

Still other approaches to incorporating PTFE as the sole or a large portion of a vascular graft have involved numerous constructions. These include constructions wherein an inner tube is surrounded by one or more other layers of tubing, foam or fiber wrapping to enhance its mechanical compliance and, for example, provide direct impermeability, or result in clotting which, after a short time, becomes impermeable. The inner tube is generally formed of PTFE, selected for its highly advantageous biocompatibility properties in the blood path. Various outer layers may consist of fibers either helically wound or electrostatically flocced, films of thin material, tape wrap generally also of thin material, or coatings. Materials used for these layers may also include impermeable polyurethane or other soluble polymer coatings, emulsions and also PTFE films.

These composite structures are in some ways similar to the earlier generation of fabric grafts made of woven or knitted Dacron or the like, and each represents an attempt to address or optimize some of the various constraints encountered in trying to replace a vessel with material which is strong, capable of long term patency and has some degree of tissue compatibility.

In general, however, conventional vascular grafts manufactured from porous polytetrafluoroethylene have limitations in surgical handling and healing.

Presently, many vascular grafts exhibit some degree of weeping or blood loss during implantation. A variety of factors effect this surgical complication, one being prewetting of vascular grafts with heparinized saline or antibiotics to render the surface thrombus and infection resistant. Prewetting of the graft results in a reduction of the hydrophobic properties with an effective increase in permeability. Cohesion of platelets and adhesion of fibrin in the graft wall can initiate the coagulation cascade resulting in thrombus formation. The thrombi are responsible for the formation of emboli in tubular prostheses with small diameters.

Native arteries and veins have a common pattern of organization made up of three layers: an internal intima, surrounded by a media, and then an external adventitia. Each of these layers has a predominant structure and cell-type. The walls of arteries are built of elastin, collagen, a non-fibrous glucosaminoglycan-rich matrix and smooth muscle cells. The microscopic structure of the artery wall correlates with the function of the various wall-layers and components.

Several studies support the belief that there is a net transport of macromolecules across the arterial wall. The transport process is controlled by diffusion, convection, and forces. Convection is associated with the hydraulic flux resulting from pressure or osmotic differences across the arterial wall. Diffusion occurs in response to a concentration driving force.

While a number of vascular grafts, or processes for preparing the same, provide for a stronger graft, such grafts do not generally possess a differential permeability effective to achieve enhanced healing and tissue ingrowth, and at the same time offer improved surgical handling.

There is a need for an in vivo implantable material device, and in particular vascular grafts which are formed as a

lamellate structure that mimics the natural artery with differential cross-section permeability composed of collagen and elastin and is acceptable to the surrounding tissue.

It remains desirable to provide prostheses or material having enhanced tissue compatibility or long term patency or growth compatibility characteristics.

SUMMARY OF THE INVENTION

This is achieved in accordance with the present invention by providing an implantable or prosthetic material with at least first, second and third regions through the wall thickness extending continuously along the length and width thereof, and wherein material of the innermost and outermost regions has a cellular compatibility property such as node size or reticulation structure, while at least one, preferably an interior, region of the wall modulates hydraulic pressure otherwise passing through the porosity of the prosthesis. The first, second and third regions join or merge continuously together along their bounding surfaces, and form a unitary wall.

The products comprising the instant invention have a very broad application in medical devices, such as vascular grafts, endovascular devices, vascular access devices, transcutaneous access devices, synthetic heart valve leaflets, artificial organ implants, etc. In a preferred embodiment, each cross-section region of the implant can be distinguished from other regions by having different pore size, pore shape and porosity. Indeed, the fibril-nodal microstructure throughout the matrix may have the internodal distance, i.e., pore size, in one section at least two to twenty times that for its adjacent sections. An *in vivo* material having three cross-section regions, for example, the internodal distance of the pores of luminal surface of PTFE vascular graft is about 20 or 30 microns with a corresponding WEP of 200 mm Hg₋₃₅ and a specific node/fibril geometry. The internodal distance of the pores of the next zone comprise a range from about 1 to about 10 microns with a corresponding WEP of 400 mm Hg or greater and a specific node/fibril geometry, preferably about 5 to 10 microns. The pore size is excellent for cell growth mediator permeability, as distinguished, for example from total impermeability which causes an undesirable state of encapsulation. Another embodiment of the present invention includes a luminal, second, and third zone of material as previously described whereby the third zone has a pore size range of 50 to 500 microns with a corresponding WEP of 100 mm Hg or less and a specific node/fibril geometry, preferably with an internodal distance of about 50 to 100, to effectively promote fibroblast tissue ingrowth, as the healing process progresses. The lamellate structure of the present invention offers a wall architecture similar in nature to that of a native vessel which contains an intima, media, and adventitia.

A further embodiment of the present invention includes *in vivo* implantable material as described above in the form of a sheet, tube or enclosure comprising a luminal, a second and a third region as previously described. Another embodiment of the present invention includes the luminal, second and third region of material as previously described with the third region being filled to provide a source location for drug delivery.

For a vascular prosthesis, the outer wall may have a porosity or regular structure of channels which is compatible with and serves as a microscaffolding structure for the growth of connective tissue. The inner face of the prosthesis on the other hand may have a smaller pore structure, optimized for attachment of a neointima for reconstituting a

natural biological flow surface at the interior of the vessel. The modulation region serves the function of blocking the direct or immediate transmission of hydrostatic pressure or fluid migration through the thickness dimension of the wall, and prevents through-growth of tissue, allowing a stratification of tissue layers to redevelop over time in a more natural fashion after the prosthesis has been implanted. Pore structure of the modulation region may be irregular, and generally is either small in size, or tortuous in path. The modulation region may also have non-existent porosity, i.e., be a continuous solid.

The prosthesis may be constructed from plural layers or tubes of material by radially nesting a first, second and third layer of material, either as tubes, wound sheets or a wrap and then coalescing the three separate bodies together into a continuous wall body in which each region through the thickness retains the structure of the starting material for that region. Preferably, the entire structure is made from PTFE, or PTFE with another fluoropolymer.

BRIEF DESCRIPTION OF THE DRAWINGS

These and other features of the invention will be understood from the figures herein wherein:

FIG. 1 is a cross-sectional image through a wall of a first embodiment of the invention;

FIG. 2 is a cross-sectional image through a wall of a second embodiment of the invention;

FIG. 3 is a cross-sectional image through a wall of a third embodiment of the invention;

FIG. 4 is a cross-sectional image through a wall of a fourth embodiment of the invention;

FIG. 5 is a cross-sectional image through a wall of a fifth embodiment of the invention;

FIG. 6 is a cross-sectional image through a wall of a sixth embodiment of the invention;

FIG. 7 is a cross-sectional image through a wall of a seventh embodiment of the invention;

FIG. 8 is a cross-sectional image through a wall of a eighth embodiment of the invention;

FIG. 9 is a cross-sectional image through the wall of a ninth embodiment of the invention; and

FIG. 10 shows a vascular prosthesis according to any of the above embodiments of the present invention.

DETAILED DESCRIPTION

FIG. 10 illustrates an implantable prosthetic member 10 according to the present invention, which, is shown in the figure as a tubular member, suitable for implantation as a vascular graft. The member 10 has an inner wall 1 and an outer wall 2 with a thickness dimension extending therebetween. As further illustrated in FIG. 10, there are at least three continuous regions adjacent to each other and extending along the entire area of the member namely, regions a, b and c, illustratively shown in the Figure as concentric strata from the inside to the outside. As described in more detail below, the successive regions a, b, c are not separate structures but are portions of the same wall, and are distinguished by their structural properties as relates in particular to aspects of porosity.

In general, each embodiment of the invention includes at least one region having a zero or sufficiently low porosity that it effectively acts as a barrier to fluid penetration or a barrier which modulates transmission of hydraulic pressure pulsations through the thin wall of the prosthesis. This barrier

region may be a completely pore-free stratum, a stratum having small pore size, or a stratum having a high density of crossed, irregular, dead end, or closed cell pores such that it carries out its modulation or barrier function. In the latter case, even large pore material may be used, but its water entry pressure (WEP) is high. This stratum may exist at the region of inner surface 1, the region of outer surface 2, or an intermediate stratum as shown by the position of region b in FIG. 10.

In material science, there is a distinction between material porosity and permeability. Porosity is a direct measure of the physical void volume contained with a boundary, whereas permeability refers to the accessibility of that void volume. Permeability is usually expressed as a rate of flow of liquid or gas per unit area, as a function of differential pressure.

In a porous, fibrous material, that part of the total porosity which is available to fluid flow is also called the "effective porosity." The pressure required to force a liquid into a pore is a function of pore size and geometry, liquid surface tension, and solid/liquid contact angle. Surface tension opposes the entry of any nonwetting liquid into a pore, and this opposition may be overcome by external pressure.

Expanded PTFE material is characterized by lengthwise-oriented fibrils interrupted by transverse nodes. The pore size in microns is typically determined by measuring fiber length between the nodes (internodal distance). To compute fibril length, the material is viewed under sufficient magnification. A fibril length is measured from one edge of one node to the edge of an adjacent node. Fibril lengths are measured from the sample to compute a mean fibril length.

Nodes and fibrils may be further characterized by their relative geometry. That is, nodes by length, width, and height; and fibrils, by diameter and length. It is the relative geometry of nodes to fibrils, as well as, internodal distance that determines porosity and permeability of porous PTFE.

Permeability to fluid flow can be determined by measuring the amount of pressure required for water to permeate the pores of the material. To compute water entry pressure (WEP) one subjects the material to an incrementally increasing water pressure until small beads of water appear on the surface. WEP is a gage which can be used to equate porosity to permeability.

Vascular graft porosity is a measure of the void fraction within the prosthesis wall and is believed to give a rough prediction of the capacity of the graft to anchor newly formed surrounding tissue after implantation, whereas permeability is associated with fluid flow through the graft wall.

Vascular permeability or hydraulic conductivity is related to material porosity. WEP is a good measuring technique to assess this trait because it closely mimics the permeation process at the blood/prosthesis interface. WEP is defined as the pressure value necessary to push water into the pores of a synthetic tubular substrate and can be classified as: High (>400 mm Hg), Medium (200–400 mm Hg), and Low (<200 mm Hg).

It has been widely accepted since the nineteenth century that the hydrostatic pressure difference across the arterial wall is capable of transporting water from the blood into the surrounding interstitial space. The view has long been held that a continuous transport of material occurs across the arterial wall, from its inner to its outer surface. Solutes flow past the endothelium gradually passing through the various arterial wall layers eventually being transferred to the lymphatics or adventitia.

The filtration coefficients of the wall are dependent on the hydraulic conductivity of both the intima and media. The

artery wall is a heterogeneous porous medium in which interstitial fluid can flow through the interstices between cells and tissue mimicking a semipermeable membrane with hydrostatic and osmotic pressure components. The osmotic pressure difference across the vessel wall is assumed to be small compared with the hydrostatic pressure or hydraulic conductivity.

More controlled healing and tissue ingrowth is achieved by providing a specific region (outer) for cell penetration, followed by a region (barrier) that does not allow free cellular penetration/permeation but instead, allows the transport of plasma solutes such as cellular mediators (proteins, growth factors, etc.) This barrier minimizes the relatively large hydraulic force present in arterial transport that retards tissue ingrowth. Reports have shown that a negative pressure exists within the perigraft space, while blood components (cells, particles, etc.) are isolated to the blood side of the device.

A vascular graft formed from the lamellate structure of the invention mimics the natural artery with a cross-section that offers differential permeability properties resulting in a healing response acceptable to the surrounding tissue.

In a prototype embodiment of the invention, a prosthesis 10 as described above was fabricated in a multi-step procedure by assembling three physically separate bodies of material together in successive strata and then joining or coalescing them into a single unit.

When a vascular prosthesis is fabricated according to this method, preferably at least one of the bodies is a tube which may, for example, be an axially-stretched tube having a porous structure of internodal space oriented transverse to its surface. Advantageously, the nodal spacing, orientation or structure of successive strata may be offset, non-matching or misaligned to introduce or enhance a barrier or hydraulic modulation effect. For example, a prosthesis may be formed by placing a first PTFE tube on a mandrel, wrapping a ribbon of PTFE in an overlapped or non-overlapped spiral winding over the tube outer surface, and then placing another PTFE 25 tube over the assembly. For this construction, the outermost tube has preferably been previously radially expanded. Heat is then applied to the assembly, optionally with a radial compressive force, to shrink back the outer tube and coalesce the three separate bodies together into a unitary 30 prosthesis. Although effectively "welded" together, there are no visible deformations, and the through-wall properties change abruptly at the interface of each stratum or region 35 with the next.

EXAMPLE 1

PTFE resin (Fluon CD-123 obtained from ICI Americas) was blended with 100 grams of "Isopar H odorless solvent (produced by Exxon Corporation) per pound of PTFE, compressed into a preform billet and extruded into a 3.5 mm 55 I.D. and 4.0 mm O.D. tube in a ram extruder having a reduction ratio of about 200:1 in cross-sectional area from billet to extruded tube. After removal of lubricant, the extruded tube was expanded and sintered, according to the method described in U.S. Pat. Nos. 5,433,909 and 5,474, 60 824, which patents are hereby incorporated by reference herein in their entirety, under various conditions to produce material with different hydraulic porosities. This produced three different tubes, denoted A, B and C, which were used 65 as starting materials for the constructions described below.

Stretch conditions and resultant hydraulic porosities are given below in Table 1..

TABLE 1

Expansion		Hydraulic Porosity	
Temp (° C.)	Rate (in/sec)	Ratio (%)	WEP (mm Hg)
(A) 320	.004	3:1	100
(B) 300	.018	3:1	200
(C) 250	7.5	2.5:1	600

Material (B) was radially expanded to a 4 mm ID on a stainless steel forming mandrel, covered with material C that had been previously dilated to a 5 mm ID, restrained to prevent longitudinal shrinkage, and transferred to an oven at 360° C. for 5 minutes, to prepare a primary lamellate. The primary lamellate was removed from the oven and allowed to cool, covered with material (A) that had been previously dilated to a 5 mm ID, restrained to prevent longitudinal shrinkage, and placed in an oven at 360° C. for 10 minutes, to prepare a final lamellate structure (material B/C/A), a cross-section of which is shown in FIG. 1.

Material (B) was radially expanded to a 4 mm ID on a stainless steel forming mandrel, covered with material (A) that had been previously dilated to a 5 mm ID, restrained to prevent longitudinal shrinkage, and transferred to an oven at 360° C. for 5 minutes, to prepare a primary lamellate. The primary lamellate was removed from the oven and allowed to cool, covered with material C that had been previously dilated to a 5 mm ID, restrained to prevent longitudinal shrinkage, and placed in an oven at 360° C. for 10 minutes, to prepare a final lamellate structure (material B/A/C), a cross-section of which is shown in FIG. 2.

Material C was radially expanded to a 4 mm ID on a stainless steel forming mandrel, covered with material (B) that had been previously dilated to a 5 mm ID, restrained to prevent longitudinal shrinkage, and transferred to an oven at 360° C. for 5 minutes, to prepare a primary lamellate. The primary lamellate was removed from the oven and allowed to cool, covered with material (A) that had been previously dilated to a 5 mm ID, restrained to prevent longitudinal shrinkage, and placed in an oven at 360° C. for 10 minutes, to prepare a final lamellate structure (material C/B/A), a cross-section of which is shown in FIG. 3.

EXAMPLE 2

Material (B) was radially expanded to a 4 mm ID on a stainless steel forming mandrel, biaxially wound with commercially available PTFE ribbon on a helix winding apparatus, and covered with material (A) that had been previously dilated to a 5 mm ID, restrained to prevent longitudinal shrinkage and placed in an oven at 360° C. for 10 minutes to prepare a lamellate structure (Material B/Biaxial wrap/Material A), a cross-section of which is shown in FIG. 4.

PTFE ribbon was biaxially wound onto a stainless steel forming mandrel, covered with material (B) that had been previously dilated to a 5 mm ID, restrained to prevent longitudinal shrinkage and placed in an oven at 360° C. for 5 minutes, to prepare a primary lamellate. The primary lamellate was removed from the oven and allowed to cool, covered with material (A) that had been previously dilated to a 5 mm ID, restrained to prevent longitudinal shrinkage and placed in an oven at 360° C. for 10 minutes to prepare a final lamellate structure (Biaxial ribbon/material B/material A), a cross-section of which is shown in FIG. 5.

Material (B) was radially expanded to a 4 mm ID on a stainless steel forming mandrel, covered with material (A)

that had been previously dilated to a 5 mm ID, restrained to prevent longitudinal shrinkage, and placed in an oven at 360° C. for 5 minutes, to prepare a primary lamellate. The primary lamellate was removed from the oven and allowed to cool, covered with a biaxial wrap of PTFE ribbon, restrained to prevent longitudinal shrinkage and placed in an oven at 360° C. for 10 minutes to prepare the final lamellate structure (Material B/Material A/Biaxial ribbon), a cross-section of which is shown in FIG. 6.

EXAMPLE 3

Material (B) was radially expanded to a 4 mm ID on a stainless steel forming mandrel, longitudinally wrapped with commercially available PTFE ribbon, and covered with material (A) that had been previously dilated to a 5 mm ID, restrained to prevent longitudinal shrinkage, and placed in an oven at 360° C. for 10 minutes to prepare a lamellate structure (Material B/Longitudinal wrap/Material A), a cross-section of which is shown in FIG. 7.

PTFE ribbon was placed longitudinally around a stainless steel mandrel, covered with material (B) that had been previously dilated to a 5 mm ID, restrained to prevent longitudinal shrinkage, and placed in an oven at 360° C. for 5 minutes, to prepare a primary lamellate. The primary lamellate was removed from the oven and allowed to cool, covered with material (A) that had been previously dilated to a 5 mm ID, restrained to prevent longitudinal shrinkage and placed in an oven at 360° C. for 10 minutes to prepare a final lamellate structure (Longitudinal ribbon/Material B/Material A), a cross-section of which is shown in FIG. 8.

Material (B) was radially expanded to a 4 mm ID on a stainless steel forming mandrel, covered with material (A) that had been previously dilated to a 5 mm ID, restrained to prevent longitudinal shrinkage, and placed in an oven at 360° C. for 5 minutes, to prepare a primary lamellate. The primary lamellate was removed from the oven and allowed to cool, covered with a longitudinal wrap of PTFE ribbon, restrained to prevent longitudinal shrinkage and placed in an oven at 360° C. for 10 minutes to prepare a final lamellate structure (Material B/Material A/Longitudinal ribbon), a cross-section of which is shown in FIG. 9.

To assess the in vivo performance of prostheses prepared in this fashion, four millimeter lamellate grafts of various configurations were implanted into the carotid and/or femoral arteries of dogs. Explants were taken at 14, 30, 60, and 180 days. The presence of an intrawall low porosity, high WEP region produced enhanced tissue ingrowth compared to material without such a region, leading applicant to believe that hydraulic forces play a role in the healing process of implantable devices.

The foregoing examples describe the preparation of a tube having enhanced properties as a vascular graft or tissue patch in which a region of high WEP in the wall modulates communication through the wall and the biological response and growth processes occurring in or contiguous to the wall. As such, it provides an improved construction applicable to a broad range of implant and surgical prostheses. The invention being thus disclosed, variations and modifications will occur to those skilled in the art and are considered to be within the scope of the invention and its equivalents, as defined by the claims appended hereto.

We claim:

1. A method of making a device, such method comprising the steps of placing at least first and second porous PTFE portions one over the other with a low porosity PTFE portion therebetween to form an adhesive-free assemblage, and

heating the assemblage to coalesce the assemblage into a unitized device.

2. The method of claim 1, wherein the device is a prosthesis and said first and second portions are tubes.

3. The method of claim 2, wherein said substantially non-porous PTFE portion is a PTFE tube, and the step of placing to form an assemblage includes the steps of placing said tubes on a mandrel, and wherein the step of heating includes heating the assemblage while it is on the mandrel so that force of shrinkage of the tubes against the mandrel when heated joins the tubes together without solvent.

4. The method of claim 1, wherein the low porosity PTFE portion has a bias orientation and a thickness below approximately one millimeter.

5. A method of forming a device, such method comprising the steps of

providing a first portion of porous PTFE,
providing a second portion of low or non-porous material surrounding said first portion,
providing a third portion of porous PTFE surrounding
said second portion, and
coalescing said first portion, said second portion and said
third portion into a single wall wherein said second
portion modulates cell growth in portions of said wall
formed by said first and third PTFE portions and limits
through penetration of cell growth.

6. A method of making a prosthetic device, the method comprising the steps of

providing first and third tubes having a cellularly penetrable structure,
providing a second permeable tube between said first and
third portion having a structure effective to limit cell
growth between said first and third portions, and
coalescing said first tube, said second tube, and said third
tube into a unitary prosthesis.

7. The method of claim 6, wherein the step of providing said first and third tubes includes the step of forming said first tube from a fluoropolymer material.

8. The method of claim 6, wherein the step of providing said second permeable tube includes the step of forming said second tube from a fluoropolymer material.

9. The method of claim 6, wherein the step of coalescing includes the step of applying heat to said first, second, and third tubes.

10. The method of claim 9, wherein said step of coalescing further includes the step of applying a radial compressive force to said third tube.

11. The method of claim 6, further including the step of radially expanding said third tube prior to the step of providing said second tube between said first and third tubes.

12. A method of making a prosthetic device, the method comprising the steps of

providing a first fluoropolymer tube,
providing a permeable fluoropolymer material having a
permeability effective for modulating hydrostatic
pressure,
wrapping said fluoropolymer material over the outer
surface of the first tube,
placing a second fluoropolymer tube over said fluoropolymer material and said first tube, and

coalescing said first and second tubes and said fluoropolymer material to form a unitary prosthesis.

13. The method of claim 12, wherein the step of coalescing includes the step of applying heat to said first and second tubes and said fluoropolymer material.

14. The method of claim 13, wherein said step of coalescing further includes the step of applying a radial compressive force to said second tube.

15. The method of claim 12, further including the step of radially expanding said second tube prior to the step of placing said second tube over said fluoropolymer material and said first tube.

16. The method of claim 12, wherein the step of wrapping includes the step of wrapping said fluoropolymer material in spiral winding over the outer surface of said first tube.

17. A prosthetic member comprising

a prosthesis wall having first, second, and third coaxial,
permeable portions,
said first and third portions having a cellularly penetrable
structure, and
said second portion positioned between said first and third
portions and having a permeability less than said first
portion to modulate cellular penetration of said first and
third portions.

18. The prosthetic member of claim 17, wherein said second portion has a porosity less than said first portion.

19. The prosthetic member of claim 17, wherein said first and third portions are continuous tubes and said second portion is a biased wrap.

20. The prosthetic member of claim 17, wherein said first and third portions are continuous tubes and said second portion is a non-biased wrap.

21. The prosthetic member of claim 17, wherein said second portion is permeable to plasma solutes.

22. The prosthetic member of claim 17, wherein said first, second, and third portions are formed of a fluoropolymer.

23. The prosthetic member of claim 17, wherein said first, second, and third portions are coalesced together to form said prosthesis wall.

24. The prosthetic member of claim 17, wherein said second portion has a water entry pressure greater than said first portion.

25. The prosthetic member of claim 17, wherein said second portion has a permeability effective for modulating hydrostatic pressure.

26. The prosthetic member of claim 17, wherein said second portion has a permeability effective to allow passage of gas and fluid at a controlled rate between said first and third portions.

27. A prosthetic member comprising

a prosthesis wall having first, second, and third coaxial,
permeable portions,
said first and third portions having a cellularly penetrable
structure, and
said second portion positioned between said first and third
portions and having a structure effective to limit cell
growth between said first and third portions.

28. The prosthetic member of claim 27, wherein said second portion is permeable to plasma solutes.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,042,666
DATED : March 28, 2000
INVENTOR(S) : Karwoski et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 1,

Line 10, delete "...patent applications having ..." and insert -- ... Patent Applications having ... --;

Line 26, delete "... United States patents and patent applications ..." and insert -- ... United States Patents and Patent Applications ...";

Column 3,

Lines 30-31, delete "... distance, i.e, pore ..." and insert -- ... distance, i.e., pore ... --;

Column 7,

Lines 42-43, delete "... C/B/A) a cross-section ..." and insert -- C/B/A), a cross-section ... --.

Signed and Sealed this

Twentieth Day of August, 2002

Attest:



Attesting Officer

JAMES E. ROGAN
Director of the United States Patent and Trademark Office